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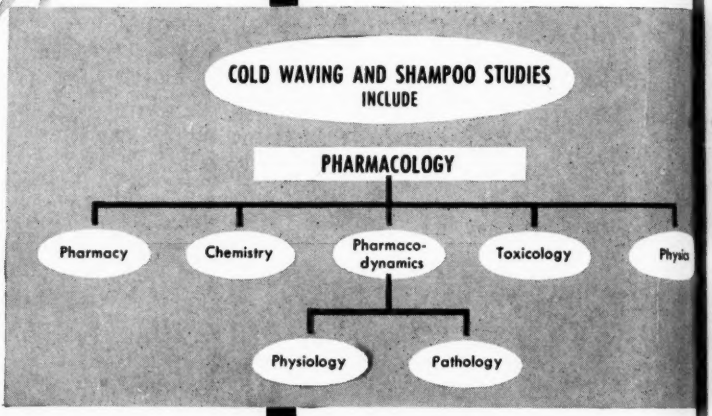

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DISSEMINATED CUTANEOUS HERPES SIMPLEX (KAPOSI'S VARICELLIFORM ERUPTION)

Report of a Case Complicated by Pregnancy and Herpetic Keratitis and Review of the Literature of Congenital Malformations Due to Dermatotropic Virus Infections in the Pregnant Mother

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IN 1887 Kaposi [1] described a varicella-like eruption for which the name "eczema herpetiformis" seemed most appropriate to him. However, the name "eczema herpetiformis" has not been generally accepted, and, instead, the dermatosis has been commonly recognized under the name "Kaposi's varicelliform eruption." In 1947 Sulzberger and Baer [2] suggested the name "disseminated cutaneous herpes simplex," and we believe that this is still the most satisfactory name for the disease.

DESCRIPTION OF THE ERUPTION

This dermatosis is an acute eruptive febrile condition which is seen most frequently as a complication of atopic dermatitis and which can complicate other primary skin diseases. It is characterized by the sudden development of lentil-sized vesicles, many of which quickly become umbilicated. They are grouped and appear in crops over a period of three or four days to a week. The affected areas become intensely swollen, edematous and at times very painful. While the eruption is confined mainly to previously diseased areas, there is, at times, extension to the normal, not previously involved skin. The eruption is accompanied usually with regional lymphadenopathy, leuko-

1. Kaposi, M.: Pathologie und Therapie der Hautkrankheiten, in Vorlesungen für praktische Aerzte und Studirende, Vienna, Urban & Schwarzenberg, 1887, p. 483.

2. Sulzberger, M. B., and Baer, R. L.: Editorial Comment, in The 1947 Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1948, p. 345.

penia, high fever, malaise, anorexia and other toxic signs and symptoms. The lesions undergo involution through desiccation, crust formation and exfoliation.

DIAGNOSIS

A definitive diagnosis depends on (1) culture of the virus on the chorioallantois of the chick, (2) corneal inoculation of the rabbit with fresh blister fluid and production of a characteristic dendritic keratitis, (3) biopsy of the lesion and observation of the characteristic histologic changes of herpes simplex and (4) evidence of an increase in the titer of complement-fixing antibodies for herpes simplex in the blood of the patient. The first specimen is taken at the beginning of or during the disease, while the second specimen is taken two to three weeks later, during convalescence. The serum in most cases shows a rise in titer during convalescence.

ETIOLOGY

The first suggestion that the disease described by Kaposi might be caused by herpes virus came in 1941 from the work of Seidenberg,[3] who inoculated material from patients into rabbits' corneas and thus produced a characteristic keratoconjunctivitis. Seidenberg's hypothesis was confirmed by the recovery of herpes simplex virus from lesions, as shown by Wenner [4] in 1944 and subsequently by Blattner, Heys and Harrison,[5] Barton and Brunsting [6] and other investigators. However, Jaquette, Convey and Pillsbury [7] considered the possibility of an association of the herpes simplex virus with staphylococci and streptococci.

Ruchman, Welsh and Dodd [8] established another link in the chain of evidence by showing that their patients had had contact with a person who had labial herpes simplex from five to 10 days preceding the onset of disseminated cutaneous herpes simplex. They recovered a filtrable agent from the cutaneous lesions of each of four patients, and this was shown by histologic methods and appropriate cross immunity tests in animals to be a strain of herpes simplex virus. An

3. Seidenberg, S.: Etiology of Pustulosis Vacciniformis Acuta: Relation to Herpes, Schweiz. Ztschr. f., allg. Path. u. Bakt. **4**:398, 1941.

4. Wenner, H. A.: Complication of Infantile Eczema Caused by the Virus of Herpes Simplex, Am. J. Dis. Child. **67**:247 (April) correction **67**:503 (June) 1944.

5. Blattner, R. J.; Heys, F. N., and Harrison, M. K.: Etiology of Kaposi's Varicelliform Eruption, J. Pediat. **27**:207, 1945.

6. Barton, R. L., and Brunsting, L. A.: Kaposi's Varicelliform Eruption, Arch. Dermat. & Syph. **50**:99 (Aug.) 1944.

7. Jaquette, W. A., Jr.; Convey, J. H.; and Pillsbury, D. M.: Kaposi's Varicelliform Eruption: Studies on Etiology, Am. J. Dis. Child. **71**:45 (Jan.) 1946.

8. Ruchman, I.; Welsh, A. L., and Dodd, K.: Kaposi's Varicelliform Eruption: Isolation of the Virus of Herpes Simplex from the Cutaneous Lesions of Three Adults and One Infant, Arch. Dermat. & Syph. **56**:846 (Dec.) 1947.

increase in complement-fixing antibodies during convalescence was demonstrated in two patients. These authors also noted that of 96 cases of cutaneous disseminated herpes simplex recorded in the literature over 75 per cent occurred in children.

McLachlan and Gillespie [9] discussed the fact that disseminated cutaneous herpes simplex can assume epidemic proportions in a dermatologic ward. They reported on 16 cases occurring in one epidemic. The fact that eight days after the first patient was admitted to the ward four new cases of the disease appeared suggested that the incubation period is eight days.

Almost all cases of disseminated cutaneous herpes simplex have occurred in patients who already had a skin disease. Unger [10] listed seborrheic dermatitis, impetigo, scabies and sycosis vulgaris in addition to atopic dermatitis as having predisposed to disseminated infection with herpes simplex virus. Simple trauma as well as the puerperium also have been followed by the eruption, according to Unger. The lesions are usually severer in the previously affected areas than in the normal skin.

DIFFERENTIAL DIAGNOSIS

Although for many years there was a tendency to associate the eruption described by Kaposi with vaccinia or variola, it is generally accepted today that the herpes simplex virus is the causal factor in characteristic cases. Nevertheless, there can be no doubt that vaccinia and variola virus also produce superimposed infection in atopic dermatitis or other skin eruptions.

Thus, Pepple, Murrell and Fowlkes [11] observed intracytoplasmic inclusion bodies similar to those of Guarnieri when the Paul test was performed. With acceptance of the Guarnieri body as evidence of variola or vaccinia, this observation seemed to support the belief that some cases which are clinically diagnosed as Kaposi's varicelliform eruption are due to the vaccinia virus. In this category also belongs the observation of Sulzberger and Baer of a case of atopic dermatitis in which smallpox vaccination was performed, contrary to the general rule that such patients should not be vaccinated, and in which the severe eruption which followed was clearly due to vaccinia virus infection, and a case of Combes and Behrman's [12] in which a superimposed vaccinia

9. McLachlan, A. D., and Gillespie, M.: Kaposi's Varicelliform Eruption: Epidemic of 16 Cases, Brit. J. Dermat. **48**:337, 1936.

10. Unger, L.: Kaposi's Varicelliform Eruption: Relation to Atopic Dermatitis, Ann. Allergy **5**:426, 1947.

11. Pepple, A. W.; Murrell, T. W., and Fowlkes, R. W.: Varicelliform Eruption of Kaposi, South. M. J. **35**:607, 1942.

12. Combes, F. C., and Behrman, H.: Eczema Vaccinatum, New York State J. Med. **43**:2283, 1943.

infection occurred in a case of sycosis vulgaris. More recently Fries and Borne [13] described cases in which vaccinia infection was superimposed on atopic dermatitis. However, we are of the opinion that in many cases one should clinically be able to differentiate between these diseases, as the eruptions produced by the variola or vaccinia virus usually are, particularly in the beginning of the rash, much more widespread and pustular than those in disseminated cutaneous herpes simplex.

PROGNOSIS

According to Blattner and associates,[5] the disease is self limited and in general the prognosis is good. However, deaths do occur, especially when acute encephalitis develops or in cases in which superimposed bacterial infection of the skin is extensive or invasive or in which other complications develop. O'Leary [14] expressed the belief that the seriousness of this disease should not be minimized, as the death rate in the literature indicates that one of every three children who have disseminated cutaneous herpes simplex die, whereas the disease is not very serious in adults. Ruchman and associates [8] found that among the 96 cases of disseminated herpes simplex recorded in the literature the death rate was 23 per cent in infants and 9 per cent in adults. It would seem to us that with modern antibiotic therapy one should be able to control to a great degree the secondary infection and thus improve the prognosis even in many of the severe cases of this disease. In this connection it is also worth remembering that there are many mild cases of abortive and relatively localized disseminated cutaneous herpes simplex.

COMPLICATIONS

Recurrences of the disease with reexposure to herpes simplex virus were described by Ruchman and associates [8] and have been observed by us.

Lane and Herold [15] discussed the difficulties in respiration, mastication and deglutition as a result of invasion of the nostrils and mouth by vesicles and bullae. Bronchitis and bronchopneumonia can readily develop, following pharyngitis and tonsillitis, complications which are not uncommon and may be serious, according to Blattner and associates.[5] King [16] reported on a patient who died eight days after otitis media

13. Fries, H. J., and Borne, S.: Vaccinial Infection in Children with Atopic Dermatitis, J. Allergy **20**:222, 1949.

14. O'Leary, P. A., in discussion on Lane and Herold, Arch. Dermat. & Syph. **50**:396, 1944.

15. Lane, C. W., and Herold, W. C.: Kaposi's Varicelliform Eruption, Arch. Dermat. & Syph. **50**:396 (Dec.) 1944.

16. King, A. D.: Kaposi's Varicelliform Eruption, Arch. Dermat. & Syph. **39**:1035 (June) 1939.

developed following severe toxemia and probably pneumonia and on another patient who died of bronchopneumonia and showed on autopsy areas of degeneration within the spinal cord.

The eyes are frequently involved. Conjunctivitis, photophobia, burning and corneal ulcers were met with by Lane and Herold.[15] The reports of Varley and Kletz [17] and Anderson [18] from England dealt with the development of corneal lesions. Barton and Brunsting [19] noted stiff neck, severe headache, burning pain in the epigastrium and incontinence of urine and feces. Hemorrhagic diarrhea,[20] anuria,[21] otitis media,[16] purulent rhinitis,[22] gangrenous slough, enlargement, abscesses and suppuration of regional lymph nodes,[9] secondary bacterial invasion,[5] scarring,[19] keloid formation,[19] alopecia,[19] pigmentation,[23] acute rapid edema,[9] purpura,[20] leukopenia and agranulocytosis [8] are other complications which have appeared in connection with disseminated cutaneous herpes simplex.

Armstrong [24] presented suggestive evidence that the virus of herpes simplex may enter the central nervous system of human beings more frequently than has been thought previously. It is in infants and children particularly that many obscure encephalopathies occur. Not uncommonly, signs such as disorientation, stiff neck, rigidity, tetanic spasticity, muscular weakness and incontinence of urine and feces indicate involvement of the nervous system. Edema and hemorrhage of the brain have been demonstrated at necropsy in some instances, according to Barton and Brunsting.[19]

REPORT OF CASE

C. J., a 24 year old white married woman, had suffered from severe atopic dermatitis since infancy. There was no family history of atopy. In November 1940, at 16 years of age, she had had an attack of Kaposi's varicelliform eruption,

17. Varley, R., and Kletz, T.: Case of Kaposi's Varicelliform Eruption (Systemic Herpes Simplex) with Dendritic Ulceration of the Cornea, Brit. J. Dermat. **61**:166, 1949.

18. Anderson, T.: Kaposi's Varicelliform Dermatosis: Virus Pyodermia, Brit. J. Dermat. **61**:157, 1949.

19. Barton, R. L., and Brunsting, L. A.: Kaposi's Varicelliform Eruption: Report of a Case, Proc. Staff Meet., Mayo Clin. **18**:199, 1943.

20. Brain, R. T., and Lewis, B.: Investigation of Virus Diseases of the Skin with Report of a Case of Kaposi's Varicelliform Eruption, Brit. J. Dermat. **49**:551, 1937.

21. Bettley, F. R.: Kaposi's Varicelliform Eruption: Some Experimental Findings, Brit. J. Dermat. **52**:222, 1940.

22. Corson, E. F., and Ludy, J. B.: Kaposi's Varicelliform Eruption: Report of 3 Cases, Am. J. Dis. Child. **50**:1476 (Dec.) 1935.

23. Lynch, F. W., and Steves, R. J.: Kaposi's Varicelliform Eruption. Arch. Dermat. & Syph. **55**:327 (March) 1947.

24. Armstrong, C.: Herpes Simplex Virus Recovered from Spinal Fluid of Suspected Case of Lymphocytic Chorio-Meningitis, Pub. Health Rep. **58**:16, 1943.

as reported to us by Dr. Allen D. King of Wilmington, Del. In 1948 reactions to intradermal tests had been positive to dust, feathers, wool, grass pollen, ragweed, peas, corn, ginger, cinnamon, wheat, rye, barley, beets, milk and penicillin.

The patient was seen again in November 1948, when she was two to three months pregnant, and she presented a severe generalized, pruritic eruption which was diagnosed as disseminated cutaneous herpes simplex superimposed on atopic dermatitis. The vesicular part of this eruption had been preceded by small groups of "blisters" on the chin. There was extensive involvement, mainly on the face, neck, nipples, upper part of the chest and upper extremities, i. e., in those areas which previously had been involved by the atopic dermatitis. The dermatologic picture consisted of umbilicated vesicles and pustules, exudation, enlarged tender lymph nodes, edema, excoriations, erythema and crusting. The temperature was 101 F., and the white blood cell count was 8,300, indicating a relative leukopenia.

The patient was hospitalized at the University Hospital. As aureomycin was not available to us at that time and because of the patient's known previous allergic reaction to penicillin, she was placed on treatment with streptomycin (2 Gm. daily by intramuscular injection) along with local therapy consisting of the application of cold wet compresses with dilute silver nitrate solution and iodochlorhydroxyquinoline (vioform®) ointment.

At the height of the acute stage of the disease the patient was somewhat comatose for two to three days, but there were no other signs or symptoms of encephalitis or other internal complication throughout the patient's hospital stay. The temperature reached 102.4 F. on the third hospital day, after which it abruptly went down with only an occasional transitory rise. The cutaneous eruption had almost completely subsided about 13 days after its inception.

Laboratory results were as follows for examination of the blood: red blood cells, 3,550,000; hemoglobin, 10 Gm. per 100 cc.; white blood cells, 8,300; polymorphonuclear leukocytes, 61 per cent; eosinophils, 11 per cent; lymphocytes, 18 per cent, and monocytes, 10 per cent. Examination of the urine gave the following values: specific gravity, 1.028; acetone, 2+; sugar, none; white blood cells, 5 to 8 per high power field, and abundant epithelial cells. Culture from pustules on agar and blood agar yielded a hemolytic Staphylococcus aureus. There were no facilities available for virus cultures. Eye cultures revealed numerous colonies of a beta (hemolytic) streptococcus and numerous colonies of hemolytic staphylococcus (mannitol and coagulase positive).

Because of the diagnosis of cutaneous disseminated herpes simplex virus infection, an eye examination was done by Dr. I. Givner the day after the patient's admission to the hospital, and no involvement was found. However, in order to forestall eye complications, prophylactic treatment of the eyes, consisting of the use of benzalkonium (zephiran®) chloride solution 1:2,000 and 2 per cent boric acid solution compresses, was instituted. Despite this, on the eighth hospital day the patient complained of a feeling of "sand" in the eyes. Several corneal ulcers were observed, and a diagnosis of bilateral herpetic (dendritic) keratitis was made. At this time the vesicles and pustules on the skin areas had disappeared. After an unsuccessful 24 hour trial of eye treatment with ether, potassium iodide and homatropine, hourly ocular instillations with aureomycin 0.5 per cent in distilled water were instituted. Within two days the eyes were decidedly improved. Treatment was continued for approximately one week and was followed by complete healing of the corneal lesions.

Except for minor fluctuations of the atopic dermatitis, the patient's convalescence was uneventful for a period of two months, when she again manifested three groups of herpetic lesions on the sides of the chin. Several of the sub-

mandibular lymph nodes became swollen and tender. To avoid a recurrence of the dissemination of the herpes simplex virus, aureomycin, which then had become available, was prescribed in doses of 250 mg. orally four times daily along with local application of 2 per cent aureomycin in qualatum® (Almay) to the lesions and the surrounding areas of normal skin three to four times daily. Within 24 hours the herpetic lesions on the chin had commenced to dry up, and healing continued through the following days. No extension of the herpes simplex infection to the areas affected by atopic dermatitis occurred under this treatment.[25]

Despite considerable doubt as to whether the pregnancy should not be deliberately terminated (see comments) the patient carried the fetus to term, and a normal baby was delivered on June 7, 1949. This infant has, up to date, developed normally, and there is no evidence of any congenital anomaly.

THERAPY

Disseminated cutaneous herpes simplex is potentially a severe and occasionally a fatal disease for which no specific treatment has existed in the past. Our brief experience with aureomycin in two cases,[25] as well as that of Bereston,[26] suggests that this drug may be an efficient and perhaps even specific form of therapy for this disease. Further support for this contention is to be found in the report of Bookman.[27]

Connor and Gonce,[28] Jaquette, Convey and Pillsbury[7] and others have reported satisfactory results with the use of sulfonamides, but, by and large, experience has been unfavorable. Lynch and Steves[23] stated that the course of the disease is only slightly affected by treatment with sulfonamides and that the eruption lasts from five to 12 days regardless of treatment. Lane and Herold[15] indicated the danger of using sulfonamides in this disease, since these drugs can reduce the leukocyte count to dangerous levels (there is characteristically an actual or relative leukopenia in this disease). Sulfonamides often control the secondary nonspecific pyodermic infection which occasionally develops in some or all of the lesions. Successful therapy in their cases consisted of application of aqueous and oily packs and of bland ointments to reduce the inflammation, rest in bed, application of an ice collar for the cervical adenopathy, forcing of fluids and administration of sedatives and antipyretics. Results of treatment with penicillin and moccasin venom in

25. Baer, R. L., and Miller, O. B.: Aureomycin Therapy of Disseminated Cutaneous Herpes Simplex (Kaposi's Varicelliform Eruption): Preliminary Report, J. Invest. Dermat. **13**:5, 1949.

26. Bereston, E. S., and Carliner, P. E.: The Treatment of a Case of Kaposi's Varicelliform Eruption with Aureomycin: Preliminary Report, J. Invest. Dermat. **13**:13, 1949.

27. Bookman, R.: Kaposi's Varicelliform Eruption: Report of a Case Treated with Aureomycin and Some Observations Regarding the Course of the Underlying Disease, J. Allergy **21**:68, 1950.

28. Connor, A., and Gonce, J. E., Jr.: Treatment of Kaposi's Varicelliform Eruption with Sulfonamides, J. Pediat. **23**:335, 1943.

one case and with moccasin venom and diphenhydramine (benadryl®) hydrochloride in the second case were equivocal, as reported by Barker and Hallinger.[29]

The failure of the eruption to respond to therapy with sulfonamides and penicillin must be regarded as further evidence suggestive of a viral cause. According to some authors, pooled serum or plasma and immune globulin have also failed to influence significantly the course of the disease. Atopic dermatitis, which is often the underlying dermatosis, is frequently temporarily benefited by the febrile intercurrent infection but usually recurs within a few weeks. This observation is in consonance with that of the improvement of atopic dermatitis during febrile infections, although this disease flares up during some nonfebrile infections (e. g., colds).

RELATION TO CONGENITAL ANOMALIES

In view of the dermatotropic nature of the etiologic agent of disseminated cutaneous herpes simplex, similar to that of the viruses causing rubeola, varicella, variola and herpes zoster, for examples, it appears fitting here to discuss the important problem of congenital anomalies in children due to a virus disease suffered by the mother during pregnancy. A great deal has been published about this in the recent medical literature, especially in connection with rubella. However, although many of the pertinent viruses are dermatotropic, we have failed to find any discussion of this exceedingly important and interesting problem in the dermatologic literature.

Until recently rubella had been considered an inconsequential disease. This concept was altered by the brilliant observations of Gregg,[30] who noted the serious effects of the disease in the pregnant mother on the fetus in utero. Gregg, an ophthalmologist, in 1941 found among babies in Australia a relatively large number of congenital cataracts. In 68 of 78 cases of congenital cataracts, the child's mother was found to have contracted rubella during pregnancy. Prior to 1939-1940 no appreciable epidemic of rubella had existed in Australia for 17 years, and the opportunity had arisen for the accumulation of a large number of rubella-susceptible young women, many of whom were in the childbearing age. A commission headed by Swan,[31] confirming Gregg's

29. Barker, L. P., and Hallinger, E. S., Jr.: Systemic Herpes Simplex (Kaposi's Varicelliform Eruption): Moccasin Venom Used in Conjunction with Penicillin in Severe Case and with Diphenhydramine Hydrochloride ("Benadryl Hydrochloride") in Mild Case, J. A. M. A. **135**:149 (Sept. 20) 1947.

30. Gregg, N. M.: Congenital Cataract Following German Measles in the Mother, Tr. Ophth. Soc. Australia **3**:35. 1941.

31. Swan, C.; Tostevin, A. L., and Black, G. H. B.: Final Observations on Congenital Defects in Infants Following Infectious Diseases During Pregnancy, with Special Reference to Rubella, M. J. Australia **2**:889, 1946.

observations, found that maternal rubella often was associated with subsequent developmental arrests of the lens and the heart in the fetus.

Carruthers [32] noted some form of deafness in 74 out of 102 children born to mothers who had had rubella during pregnancy. Gregg, Blairs, Heseltine, Machin, Vickery and Meyers [33] reported the occurrence of deaf-mutism in 85 of 130 children with congenital defects whose mothers had had rubella during pregnancy.

Congenital dental abnormalities, including particularly retardation of eruption of teeth, were discovered by Evans [34] in 33 of 34 babies whose mothers had had rubella during pregnancy.

Gregg and associates [33] expressed the conclusion that apparently children are not affected when the maternal infection occurs after the fourth month of pregnancy. However, Ingalls and Gordon [35] stated the opinion that this may not be entirely correct, as defects of an entirely different nature would be expected to follow the disease if it occurred in the second and third trimesters of pregnancy. Thus, for example, entirely different technics (e. g., radiologic) would have to be employed to demonstrate such congenital defects as spina bifida.

Mental defectiveness,[36] glaucoma and microphthalmia have been observed in addition to the other previously listed defects. All these anomalies may occur singly or in combinations. The birth weight of a large number of affected children is below normal average. Their general physique is generally below standard. Many of the children are late in sitting up and in walking, for example. It is possible that abortions, miscarriages, stillbirths and deaths of young children may occur as a result of maternal rubella during early months of pregnancy. The cause of abortions and miscarriages is thought by some to be the high fever, whereas others believe it is the organisms, toxins or low oxygen and high carbon dioxide concentrations which produce contractions of the uterus. There is no evidence to show that the occurrence of maternal rubella during one pregnancy will affect the child of a subsequent pregnancy. There may be feeding difficulties. No relation seems to exist between severity of maternal infection and the nature of the defect

32. Carruthers, D. G.: Congenital Deaf-Mutes as a Sequela of a Rubella-Like Maternal Infection During Pregnancy, M. J. Australia **2**:315, 1945.

33. Gregg, N. M.; Blairs, W. R.; Heseltine, M.; Machin, A. E.; Vickery, D., and Meyers, E.: The Occurrence of Congenital Defects in Children Following Maternal Rubella During Pregnancy, M. J. Australia **2**:122, 1945.

34. Evans, M. W.: Congenital Dental Defects in Infants Subsequent to Maternal Rubella During Pregnancy, M. J. Australia **2**:225, 1944.

35. Ingalls, T. H., and Gordon, J. E.: The Epidemiologic Implications of Development Arrests, Am. J. M. Sc. **214**:322, 1947.

36. Patrick, P. R.: Report of Survey of Children Born in 1941 with Reference to Congenital Abnormalities Arising from Maternal Rubella, M. J. Australia **1**:421, 1948.

in the child. Hagstromer [37] reported two cases of congenital malformations, including harelip, partial cleft palate and rudimentary right ear, among others, manifested in the children after already immune mothers had been exposed to measles in early pregnancy. In both cases, the pregnant women had remained free from measles, having had attacks during their childhood.

However, not every case of rubella in pregnant women is followed by congenital defects, as was shown by the report of Gregg and associates [33] of six cases of maternal rubella during pregnancy after which the children turned out to be normal in all respects. While most observers agreed with Gregg that there is a striking incidence of abnormalities of pregnancy during the first trimester, there were many who expressed the opinion that previous statistics were distorted. Fox and Bortin,[38] in a review of 11 pregnant women who had rubella, noted only a 9 per cent incidence of congenital abnormalities. Moreover, they pointed out that one must be very careful in attributing a causal relation to rubella for all the defects found in the various surveys, as it appears almost sure that some of the defects would have occurred even if the mothers had not had rubella. On the other hand, the children should be followed to the age of 12 to 15 years, if necessary, so that all important abnormalities might be observed, as it is obvious that some defects—such as, for example, deafness—following rubella are very difficult to evaluate in infants.[33]

An interesting editorial appeared in *The Journal of the American Medical Association* [39]:

> Fetal injury is believed to occur as a result of passage of rubella virus through the placental barrier, thereafter exerting a direct effect on early somatic fetal development. Paradoxically, rubella produces the same result when it occurs and subsides even before conception. Retention of the virus in maternal tissues and its later passage through the placenta to the fetus may occur. Other diseases occurring in early pregnancy and in the immediate preconception period, particularly infectious mononucleosis, are stated to result in congenital defects. Both restricted maternal diet and fetal irradiation are known to be capable of causing anomalous development in offspring of laboratory animals.

With the belief that later effects of malnutrition were related to changes in plasma proteins, Gillman, Gilbert, Gillman and Spence [40]

37. Hagstromer, A.: Two Cases of Congenital Malformations After Exposure to Measles in Early Pregnancy of Already Immune Mothers, Acta pædiat. **35**:247, 1948.

38. Fox, M. J., and Bortin, M. M.: Rubella in Pregnancy Causing Malformations in the Newborn, J. A. M. A. **130**:568 (March 2) 1944.

39. Congenital Defects, editorial, J. A. M. A. **138**:653 (Oct. 30) 1948.

40. Gillman, J.; Gilbert, C.; Gillman, T., and Spence, L.: A Preliminary Report on Hydrocephalus, Spina Bifida and Other Congenital Anomalies in the Rat Produced by Trypan Blue, South African J. M. Sc. **13**:47, 1948.

treated female rats with trypan blue because of its plasma albumin–binding properties. In a total of almost 700 offspring, approximately 20 per cent presented gross macroscopic malformations detectable at birth. These included hydrocephalus, spina bifida and eye defects, among others. Among all offspring high neonatal mortality, reduction in size of litters, low birth weights and a general retardation of postnatal development occurred.

These authors stated the opinion that there is a parallel in the development of congenital defects in offspring of trypan blue–treated rats and in infants born after maternal rubella infection. They demonstrated that the trypan blue in maternal rats did not enter the fetus, the amniotic epithelium or amniotic fluid. All embryonic tissues apart from the yolk sac were free from trypan blue particles. This observation furnishes additional evidence against the already debatable hypothesis of passage of virus through the placental barrier. The experiments of Gillman and associates [40] tended to demonstrate that the effects of trypan blue—and, by inference, rubella virus—are not direct effects on the fetus but that these agents cause remote metabolic states which subsequently interfere with fetal development.

Hurst [41] suggested that the causative factor of rubella acts primarily on the vascular tissue, as evidenced, for example, by changes in the renal glomeruli on postmortem examination. He made the hypothesis that cataracts result from interference with the nutrition of the lens fibers brought about by changes of the hyaloid artery. Possibly cardiac abnormalities are due to a similar alteration in the wall of the ductus arteriosus, which prevents closure.

Gasser and Schwarz [42] reported peculiar calcifications in the brain, eye and liver, some with signs of chronic inflammation, on histologic examination in a baby aged 8 months whose mother had had an eruptive disease, allegedly German measles, in the third month of pregnancy. It was felt that the cerebral calcification was probably a residue of prenatal encephalitis.

Arey [43] indicated that the lens of the eye, the cochlea and the semicircular canals are completed early in the third month of gestation. However, the interatrial septum is not entirely completed until the foramen ovale is closed at the time of birth. The reason that the defects

41. Hurst, cited by Swan, C.: A Study of 3 Infants Dying from Congenital Defects Following Maternal Rubella in the Early Stages of Pregnancy, J. Path. & Bact. **56**:289, 1944.

42. Gasser, C., and Schwarz, E.: Fetal Deformities with Abnormal Calcifications Following Infections (Toxoplasmosis, German Measles) During Pregnancy, Helvet. paediat. acta **2**:351, 1947.

43. Arey, L. B.: Developmental Anatomy: A Textbook and Laboratory Manual of Embryology, ed. 4, Philadelphia, W. B. Saunders Company, 1941.

occur mainly in infants whose mothers had rubella in the first three months of pregnancy is that the cells may be more susceptible then or that the barrier of the placenta becomes more effective after this time. The resulting anomaly would then be expected to be a function of the stage of development at which the agent is active. Patency of the cardiac septum cannot come into being as a developmental arrest after the septum has closed, nor can an imperforate anus after the anal membrane has perforated.

Prendergast [44] cited a case of microphthalmos in a fetus following chickenpox in early pregnancy.

Numerous authors, including Wesselhoeft,[45] emphasized the fact that many other diseases which afflict the mother during the early months of pregnancy are capable of causing fetal deformities. Among these diseases are rubeola, mumps, herpes zoster, scarlet fever, varicella, influenza, hepatitis and poliomyelitis. It is noteworthy that most of these are virus diseases.

Swan and associates [46] reported that of two cases of varicella during pregnancy, one which occurred during the seventh month resulted in the development of congenital heart disease and nevus formation; and two women who had herpes zoster during pregnancy gave birth to infants with deaf-mutism, heart disease and myelocele, among other defects. They also described one case in which scarlet fever in the mother during pregnancy produced a congenital obliterative defect of the bile ducts in the child.

Bull [47] stated that smallpox, although rarely seen in pregnancy, terminates the pregnancy in 30 to 69 per cent of cases; the later the stage of pregnancy, the more likely the termination. Intrauterine infection is common, and the child may be born pockmarked. According to this author scarlet fever and whooping cough are known to interrupt pregnancy, too, and evidence suggests that the risk to the fetus in maternal poliomyelitis is, as in German measles, high if the disease occurs in the first three months of pregnancy and less in later months.

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44. Prendergast, J. J.: Congenital Cataract and Other Anomalies Following Rubella in Mother During Pregnancy: California Survey, Arch. Ophth. **35**:39 (Jan.) 1946.

45. Wesselhoeft, C.: Rubella (German Measles), New England J. Med. **236**: 978, 1947.

46. Swan, C.; Tostevin, A. L.; Moore, A.; Mayo, E., and Black, G. H. B.: Congenital Defects in Infants Following Infectious Diseases During Pregnancy with Special Reference to Relationship Between German Measles and Cataract, Deaf-Mutism, Heart Disease, and Microcephaly and to Period of Pregnancy in Which Occurrence of Rubella Is Followed by Congenital Abnormalities, M. J. Australia **2**:201, 1943.

47. Bull, C.: The Effect on the Fetus of Diseases of the Mother During Pregnancy, Arch. Pediat. **62**:289, 1945.

It is interesting to note that at the time of the mass smallpox vaccination in New York city in April 1947, a group of over 700 pregnant women, many of whom were in their first trimester, were vaccinated in the antepartum clinic of the Sloane Hospital for Women. On the basis of the results observed in this study, it was concluded by Bellows, Hyman and Merritt [48] that smallpox vaccination during pregnancy does not increase the incidence of congenital malformations, stillbirths, abortions or infant deaths.

At the present time, the only positive measure for prevention of anomalies, according to Aycock and Ingalls,[49] is deliberate exposure to such diseases as rubella and varicella before the child-bearing period. It appears possible that inoculation with rubella virus may become part of the future program of preventive medicine just as is vaccination against smallpox. Such a possibility awaits the development of suitable technics. While many physicians have accepted the available evidence as sufficient grounds for termination of the pregnancy, this procedure is likely to be illegal in many states or countries, inasmuch as danger to the life of the mother is a legal prerequisite for such a procedure and the mother's life is, as a rule, in no way endangered. However, there is an equally large group of physicians who feel that there is no justification for a therapeutic abortion when a woman has one of the exanthems during pregnancy, even if this occurrence takes place during the first trimester; e. g., Fox and Bortin [38] did not express agreement with the conclusions of Erickson [50] and Swan and associates,[46] who suggested that the pregnancy should be terminated in such cases.

This entire subject is deserving of much intensive study, not only by pediatricians and immunologists but also by dermatologists, who, even though they see a limited number of cases of acute infectious exanthems, see a large number of cases of zoster, herpes simplex, and the like, some of them in pregnant women. This far-reaching question can be correctly answered only when there are adequate statistical studies to establish the specific risks to the fetus from the various dermatotropic virus infections at all stages of pregnancy. Available data indicate that the first three months of gestation constitute by far the most vulnerable period for the fetus. One wonders whether there is any connection between certain nevi including hemangiomas, large, hairy and/or pigmented nevi, ichthyosis and certain congenital ectodermal defects (albinism and anhydrosis, for example) occurring in the newborn infant

48. Bellows, M. T.; Hyman, M. E., and Merritt, K. K.: Effect of Smallpox Vaccination During Pregnancy, Pub. Health Rep. **64**:319, 1949.

49. Aycock, W. L., and Ingalls, T. H.: Maternal Diseases as a Principle in the Epidemiology of Congenital Anomalies, Am. J. M. Sc. **212**:366, 1946.

50. Erickson, C. A.: Rubella Early in Pregnancy Causing Congenital Malformation of Eyes and Heart, J. Pediat. **25**:281, 1944.

and virus disease in the mother during pregnancy. Also the dermatologist must ask himself whether the evidence that herpes zoster and varicella in the pregnant mother can produce congenital defects in the infant does not suggest that attacks of localized labial, progenital and other types of herpes simplex or disseminated cutaneous herpes simplex can be sources of damage to the fetus in the mother. It appears, however, most unlikely that other dermatologic virus diseases such as verruca vulgaris, verruca plana and molluscum contagiosum would be the cause of damage to the fetus.

In the case of patient C. J., reported in this paper, both the obstetric and the pediatric experts were divided in their opinions as to whether artificial termination of the pregnancy should be instituted. The patient herself eventually decided against having her pregnancy terminated. Fortunately the infant, 9 months old at the time of writing this report, appears to be a perfectly normal child.

SUMMARY

A case is reported of disseminated cutaneous herpes simplex occurring during the second to third month of pregnancy and complicated by herpetic keratitis. The diagnostic features, etiology, prognosis, complications and therapy of the disease are discussed. A review is given of congenital defects which have been reported to occur as a consequence of certain diseases, especially of those due to dermatotropic viruses in the pregnant mother. In the case reported here, severe disseminated cutaneous herpes simplex infection (Kaposi's varicelliform eruption) during the first months of pregnancy had not produced any detectable congenital defects in the infant, observed for nine months following birth.

SKIN TESTS IN VARIOUS INFECTIOUS AND PARASITIC DISEASES

A Summary in Table Form *

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THE SKIN often enables one to ascertain whether or not a person has had adequate exposure to a particular infectious or parasitic agent. This ability of recording more or less permanently experiences which the skin has undergone has been called "mnemodermie." It will be impossible here to discuss the technical and immunologic details of the various skin test procedures. This has been done adequately in the available textbooks.[1] However, a few introductory remarks appear necessary to facilitate the understanding of the tables presented.

In infectious and parasitic diseases, skin tests can be utilized for the following purposes: (1) to establish whether exposure has taken place, (2) to establish whether the skin is in a state of relative susceptibility or resistance and (3) to help in making the diagnosis and prognosis.

The altered reactivity of the skin which occurs after clinical or subclinical exposure to certain infections or infestations may, with or without demonstrable reexposure, last for varying periods. While it often lasts for many years and sometimes for life, it does not necessarily persist indefinitely. Then, too, after originally having been established at a certain level, it may show changes in the direction of either increased or decreased reactivity and at times may revert to the status which existed before adequate exposure took place; i. e., it may revert to negativity or positivity.

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* In part based on the tables in Sulzberger, M. B., and Baer, R. L.: "Office Immunology Including Allergy: A Guide for the Practitioner," Chicago, The Year Book Publishers, Inc., 1947.

1. (a) Sulzberger, M. B.: Dermatologic Allergy: An Introduction in the Form of a Series of Lectures, Springfield, Ill., Charles C Thomas, Publisher, 1940. (b) Sulzberger, M. B., and Baer, R. L.: Office Immunology, Including Allergy: A Guide for the Practitioner, Chicago, The Year Book Publishers, Inc., 1947.

Some of the changes in skin reactions are spontaneous or due to factors which are unknown. Others, however, are the result of recognized influences. For example, cachectic and debilitating states, certain acute infectious diseases, such as measles and typhoid, and overwhelming infections have been shown to reduce or abolish, in a nonspecific manner, skin sensitivity to various allergens. When the skin is incapable of reacting one speaks of "anergy," and the particular type of anergy cited is referred to as negative (nonspecific) anergy, as the reduction or abolishment of skin sensitivity usually extends to a wide range of allergens which are immunologically unrelated to one another as well as to the organism causing the disease in question.

On the other hand, one speaks of positive (specific) anergy when the reduction or abolishment of reaction is due to a very high and specifically acquired degree of immunity. The best example of this

TABLE 1.—*Important Types of Skin Reactions in Infections and Infestations*

Type	Quantity Used	Technic of Administration	Reaction Time	Morphologic Manifestations	Subjective Manifestations	Significance of Positive Reaction
Immediate urticarial reaction	0.01-0.02 cc.	Intracutaneous	10-30 minutes	Urticaria and flare	Itching	Sensitivity based on adequate previous exposure
Delayed tuberculin type reaction	0.1 cc.	Intracutaneous	24-72 hours	Erythema and induration	Usually none; sometimes pain and heat	Sensitivity based on adequate previous exposure
Very late reaction	0.1 cc.	Intracutaneous	2-4 weeks	Nodule, erythema, ulceration	Usually none	Sensitivity based on adequate previous exposure
Delayed toxin reaction	0.1 cc.	Intracutaneous	24-96 hours	Erythema alone or with induration	Usually none	Susceptibility based on lack of adequate previous exposure

type of anergy is the reaction in sarcoidosis to tuberculin. Here the reduction in sensitivity is confined to the specific allergen tuberculin. The reason for calling this type of anergy "positive" is that the lack of reaction is presumably due to the presence of certain immunizing or neutralizing substances in the skin, the so-called anticutins.

As will be seen from table 1, the skin reactions encountered in infections and infestations fall into several characteristic categories:

The immediate urticarial reaction is oftenest seen in infestations by parasites. It is negative in those not adequately exposed, but the incidence of positive reactions in those exposed varies greatly with the particular allergenic material. Urticarial reactions to the allergens of certain parasites, i. e., those of helminthic origin, are of limited value because of the wide range of cross reactions which occur.

The delayed (twenty-four to forty-eight hour) tuberculin type reaction is the most usual response produced by allergens of bacterial,

fungous and viral origin. This reaction is negative in those who have not been previously exposed and tends to be positive in those who have been adequately exposed.

The third type of skin reaction listed in table 1 is that which we have called the "very late reaction." This reaction is at present of practical use only with regard to sarcoidosis and leprosy; it is positive only in persons adequately exposed but can be negative in exposed as well as nonexposed subjects.

Another important type of reaction is what we have called the "delayed toxin reaction." The significance of positive and negative reactions of this type is in direct contrast to that of the tuberculin type reaction, the bacterial toxin producing a positive reaction only in susceptible persons while those who previously have been adequately exposed and have thus been immunized will usually show a negative reaction.

It must be realized that the value of some skin tests may diminish when they are repeated one or more times. This is especially true in the diagnosis of some helminthic diseases, when the exposure to a single intradermal injection of the test allergen may be sufficient to sensitize the skin to the allergen. The skin test with pertussis agglutinogen, which will be discussed herein, is another example of this phenomenon.

The significance of skin tests is further limited by the occurrence of cross reactions to different allergens. Group specificity and not species specificity is characteristic of the sensitivity to trichophytin. This extract produces reactions in many subjects who have been adequately exposed to trichophytons, microsporons and epidermophytons, all of which have, in addition to species-specific factors, some common denominator which sensitizes to trichophytin. Also, as stated above, skin reactions produced as a result of parasitic infestations almost invariably are associated with cross sensitization to the extracts of many other related parasites.

The skin test not only may itself bring about sensitization to the test material but also even in the previously sensitized subject can cause changes in the immunologic state existing prior to performance of the test. For example, a single skin test with pertussis agglutinogen may produce not only a significant rise in the serum agglutinin titer, even though agglutinins were absent before the skin test, but also a feeble reaction to a second test as well. A third skin test may bring about an agglutinin titer as high as 1 : 640 to 1 : 1,280. Therefore it is advisable in certain infections and infestations to take a blood sample for agglutination and other serologic tests before or at the time the skin test is performed.

TABLE 2.—*Skin Tests in Infections and Infestations*

Disease	Report(s) in the Literature	Organism	Material	Availability of Material	Type of Reaction	Comment
Actinomycosis	Neuber; Cope	Actinomyces bovis	Actinomycin (vaccine or culture filtrate)	Not commercially	Delayed tuberculin type	Said to be specific and diagnostically useful
Ascariasis	Bachman; Baron and Brunner; Brunner, Altman and Bowman	Ascaris lumbricoides	Ascaris antigen (saline extract)	Not commercially	Immediate	Cross sensitizations with other helminthic infestations (e. g. uncinariasis, oxyuriasis, trichuriasis, schistosomiasis, trichinosis); skin test itself produces sensitization
Blastomycosis	Martin; Martin and Smith, March 1939 and April 1939	Blastomyces dermatitidis	Blastomycin (vaccine or culture filtrate)	Not commercially	Delayed tuberculin type	Positive reaction makes past or present infection likely; negative reaction does not rule out infection; cross reactions occur with histoplasmin, coccidioidin, haplosporangin and very rarely with sporotrichin; negative reactions occur in patients with proved active blastomycotic infection (negative anergy?)
Chancroid	Dienst and Gilkerson; Heyman	Hemophilus ducreyi	H. ducreyi vaccine	Lederle	Delayed tuberculin type	Positive reaction indicates past or present infection; occurs in 70-80% or more of infected subjects; negative reaction does not rule out infection
Coccidioidosis	Katzenstein; Haynes and Hess; Tucker; Clark and Gilmore; Cheney and Denenholz; Smith and others	Coccidioides immitis	Coccidioidin (culture filtrate)	Not commercially	Delayed tuberculin type	Positive reaction indicates past or present infection; reaction may become negative 6-12 months after infection; negative reaction may occur during dissemination (negative anergy); cross reactions occur with histoplasmin, blastomycin and haplosporangin
Diphtheria		Corynebacterium diphtheriae	Schick toxin	From many sources	Erythema and induration still positive at 4 or more days	Positive reaction indicates susceptibility to toxin; negative reaction indicates probable lack of susceptibility; test is not reliable in regard to susceptibility to skin diphtheria; pseudo-Schick reaction must be ruled out (reaction negative after 3 days)
Echinococcosis	Grana; "Casoni Test: A Review"; Casoni; Pontano	Echinococcus granulosus	Hydatid fluid of animal or human origin	Not commercially	Immediate (Pontano)	Positive reaction in 75% of echinococcosis patients but cross reactions occur with other helminthic infestations, cancer of the liver and jaundice
					Delayed tuberculin type (Casoni)	Positive reaction in 50% of echinococcosis patients but highly specific; skin test itself sensitizes
Epidermophytosis		Trichophytons, epidermophytons, achorions, microsporons	Trichophytin (culture filtrate; fungi are triturated)	Lederle, Lilly, Arlington, Bischoff	Delayed tuberculin type	Positive reaction very common; indicates past or present infection; is not diagnostic; negative reaction does not rule out superficial fungous infection but throws strong doubt on "id" diagnosis
					Immediate	Reaction likely to be positive in trichophyton purpureum infection, erysipelas-like "ids" and atopic dermatitis

Filariasis	Culbertson, Rose and Demarest, March 1944, p. 152 and p. 156; Oliver-González and Hernández Morales; Saunders, Bianco and Jordan; Wharton; Bozicevich and others; Zelig: Franks, Chenoweth and Stoll	Wuchereria bancrofti	Saline extract of dried dirofilaria immitis	Not commercially	Immediate	Positive reaction in about 70% to 90% of filariasis patients but cross reactions with other helminthic infestations (uncinariasis, ascariasis, trichuriasis, schistosomiasis, onchocerciasis, oxyuriasis)
					Delayed tuberculin type	Not as sensitive as immediate reaction; occasional delayed reactions without immediate reactions
Glanders		Malleomyces mallei	Mallein (culture filtrate)	Not commercially	Delayed tuberculin type	Said to be specific; becomes positive 14-40 days after infection
Granuloma inguinale	Kornblith; Anderson, DeMonbreun and Goodpasture, January 1945 and March 1945; Anderson, Goodpasture and DeMonbreun	Klebsiella granulomatis (Donovan body)	(*a*) Vaccine	Not commercially	Delayed tuberculin type (24 hours)	Not yet generally accepted but appears to be specific
			(*b*) Filtrate of infected yolk			
			(*c*) Capsular substance			
Herpes simplex	Nagler, April 1944 and June 1946	Herpes simplex virus	Amniotic fluid of infected chick embryo	Not commercially	Delayed tuberculin type	Said to be specific and positive in patients with herpes simplex eruption
Histoplasmosis	Christie and Peterson; Sontag and Allen; Groover and others; Parsons and Zarofonetis	Histoplasma capsulatum	Histoplasmin (vaccine or culture filtrate)	Not commercially	Delayed tuberculin type	Significance of positive reaction to skin test not fully established; cross reactions with blastomycin, coccidioidin, haplosporangin; negative reactions may occur in advanced cases (negative anergy)
Leishmaniasis	Dostrovsky and Sagher; Sagher, May 1947 and June 1947	Leishmania tropica	Leishmania vaccine	Not commercially	Delayed tuberculin type	Positive reactions in 92% of infected patients; nonspecific reactions in 6%; not yet generally accepted
Leprosy	Dharmendra and Lowe; Salazar Mallen and Rosas Prieto; Olmos-Castro and Arcuri; Dharmendra; Fernández and Mercau	Mycobacterium leprae	(*a*) Lepromin (saline suspension of leprous tissue)	Not commercially	Very late reaction (2-4 weeks)	Tends to be positive in tuberculoid type and negative in lepromatous type; thus has diagnostic and prognostic significance; some observers report that skin test itself may produce positive reaction in second or later test
			(*b*) Suspension of dried triturated defatted bacilli in saline solution		Delayed tuberculin type	Same as with *a*
Lymphogranuloma venereum	Pollard and Witka; Hickam; Heyman; Nigg, Grace and Hilleman	Lymphogranuloma venereum virus	(*a*) Infected chick embryo vaccine	Squibb, Lederle	Delayed tuberculin type	Specific but cross reactions occur with psittacosis antigen; positive reaction indicates past or present infection; negative reaction indicates almost always lack of infection; negative anergy occurs; positive reaction must be 0.7 cm. larger than control reaction
			(*b*) Human antigen	Not commercially	Delayed tuberculin type	Same as for *a*, but no control test done
			(*c*) Mouse brain antigen	Not commercially	Delayed tuberculin type	No longer used; produces more nonspecific reactions
Moniliasis		Candida albicans	Oidiomycin (culture filtrate; fungi are triturated)	Lederle	Delayed tuberculin type	Of no practical use except as a control material for trichophytin test with Lederle material; no reaction in some cases of proved C. albicans infection of the skin

TABLE 2.—*Skin Tests in Infections and Infestations—(Continued)*

Disease	Report(s) in the Literature	Organism	Material	Availability of Material	Type of Reaction	Comment
Mumps	Enders, Cohen and Kane; Enders, Kane, Maris and Stokes; Pearson; Muntz, Powell and Culbertson	Mumps virus	Infected allantoic fluid or suspension of heat-inactivated infected parotid gland of monkey	Not commercially	Delayed tuberculin type (24-36 hours)	Reaction becomes positive some weeks after onset of disease in about 80% to 90% of known cases; positive reaction is larger than 1.0-1.5 cm. in diameter; positive reaction indicates immunity in 95% of cases; reaction must be read and measured in daylight; it sometimes fades before 48 hours; skin test itself may produce positive reaction in second or later test
Reiter's disease	Storm-Mathisen	Unknown	Inactivated lymph node suspension or joint exudate	Not commercially	Delayed tuberculin type	Not yet generally accepted—only reported by one author in small series of cases; said to be specific
Sarcoid		?	Tuberculin	Many sources	Delayed tuberculin type	In most cases positive anergy, i. e., negative reaction to high concentrations
			Kveim material (suspension of sarcoid tissue, including lymph node, spleen, etc.)	Not commercially	Very late reaction (2-4 weeks)	Specificity probably quite high—but still under discussion; reaction consists of very persistent nodule which at times breaks down and leaves ulcer
			BCG vaccine	Not commercially	Very late reaction (2-4 weeks)	Specificity probably quite high—but still under discussion; reaction consists of very persistent nodule which at times breaks down and leaves ulcer
Scarlet fever		Streptococcus scarlatinae	Dick toxin	Many sources	Erythema only (24 hours)	Positive reaction is 1 cm. or more in diameter; usually indicates susceptibility to toxin; negative reaction indicates probable lack of susceptibility; some investigators insist on use of heat-killed control material
Sporotrichosis	Katzenstein	Sporotrichum schenckii	Sporotrichin (vaccine or culture filtrate from S. schenckii)	Not commercially	Delayed tuberculin type	Positive reaction is usually evidence of past or present infection; there may be very rare cross reactions with blastomycin; negative reaction usually indicates lack of infection, but rare negative reactions in infected subjects are said to occur (positive or negative anergy?)
Syphilis		Treponema pallidum	Luetin (suspension of infected organ material)	Not commercially	Delayed tuberculin type	Not very specific and of almost no clinical value; positive reactions occur sometimes in late secondary syphilis and more frequently in tertiary syphilis; negative reactions of no significance; nonspecific reactions are produced by administration of iodides, agar, bromides(?)
Trichinosis	Shookoff, Birnkrant and Greenberg; Harrell, Horne, Aikawa and Helsabeck; Frisch, Whims and Oppenheim, January 1947, p. 16 and p. 29	Trichinella spiralis	Trichinella antigen (saline extract of trichinella)	Lederle, Lilly	Immediate	Positive reaction usually indicates past or present infestation with trichinella; negative reaction does not rule out past or present infestation; cross reactions occur with ascariasis, echinococcosis, trichuriasis, oxyuriasis
					Delayed tuberculin type	Occurs less commonly than urticarial reaction and is less commonly used; skin test itself may produce sensitization
Trichomoniasis	Adler and Sadowsky	Trichomonas vaginalis	Trichomonas antigen (aqueous extract of flagellates)	Not commercially	Delayed tuberculin type	Of little practical use and not generally accepted—only one report available; 80% positive reactions in known infected subjects and about 10% in subjects without known present infection

			extract of flagellates)			subjects and about 10% in subjects without known present infection
Tuberculosis		Mycobacterium tuberculosis	Tuberculin (O. T. K.)	Many sources	Delayed tuberculin type	Positive reaction indicates past or present infection; negative reaction usually indicates lack of past or present infection but may be due to positive (specific) or negative (nonspecific) anergy; positive tuberculin reaction as a rule signifies not only skin sensitivity but also some degree of resistance to M. tuberculosis; quantitative testing useful in some cases; repeat test if indicated
			Purified protein derivative (P. P. D.)	Parke, Davis; Sharp & Dohme		
			Tuberculin (O. T. K.) for patch test	Lederle	Vesiculo-papular	Significance of positive and negative reactions as with intracutaneous test; test with caution, particularly in children, if there is evidence of involvement of organs other than the skin; however, patch test is not quite as sensitive as intracutaneous test
Tularemia	Foshay	Pasteurella tularensis	Detoxified heat-killed suspension of Past. tularensis	Not commercially	Delayed tuberculin type	Positive reaction indicates past or present infection—may start as early as second day; negative reactions in infected subjects occur in terminal stage (negative anergy?); negative reaction usually indicates lack of past or present infection
			Antitularemia serum (goat, horse)	Sharp & Dohme	Immediate	Significance disputed
Typhus (epidemic type)	Clavero and Pérez Gallardo; Sohier, Parnet and Chon; Fabiani; Mutsaars	Rickettsia prowazeki	Formaldehyde-killed saline suspension of infected rabbit lung	Not commercially	Delayed tuberculin type	Significance not yet established; one half or more of infected subjects are said to have positive reaction two months after infection; negative reaction is said to indicate lack of past infection
Undulant fever (brucellosis)	Urschel; H. J. Harris; Eisele; Darley and Gordon; Spink; Huddleson	Brucella abortus, brucella melitensis, Brucella suis	Brucella vaccine (saline suspension of heat-killed organisms)	Many sources	Delayed tuberculin type	Positive reaction indicates past or present infection; negative reaction usually indicates lack of past or present infection but also occurs in infants, in aged persons and overwhelming infection (5-10%); more sensitive test than with brucellergen; also more likely to produce severe local and systemic reactions; (dilute 1:10?) Br. abortus vaccine is preferable to mixed brucella vaccine
			Brucellergen (brucella protein nucleate)	Sharp & Dohme	Delayed tuberculin type	Positive reaction usually indicates past or present infection; negative reaction usually indicates lack of past or present infection but also occurs in overwhelming infection, in infants and the aged (5%); rarely produces local lymphangitis and lymphadenitis and fever; both test materials may produce positive skin reaction at second or later test and may stimulate production of agglutinins and opsonins, even without actual infection (take blood for serologic tests before skin test)
Whooping cough	Sauer and Markley; Felton and Flosdorf; Felton, Smolens and Mudd	Hemophilus pertussis	H. pertussis agglutinogen	Not commercially	Delayed tuberculin type	Positive reaction usually indicates immunity; negative reaction usually indicates susceptibility; false positive and negative (30%) reactions occur; skin test can produce rise in serum agglutinins and a weak reaction to a second skin test

Certain skin tests are not always wholly without side effects. Particularly in tests for the tuberculin type response pronounced local reactions in severity up to necrosis as well as lymphangitis, regional lymphadenitis and febrile systemic reactions may occur. In tests for the very late reaction persistent plaques with ulceration may occur. Moreover, skin reactions in areas removed from the test site have also been observed. Among these are the "id" reactions after injections of trichophytin and focal reactions in the pleura, meninges, eyes, skin or other focus after injections of tuberculin. The dangers of these undesirably severe reactions can be minimized by testing with serial dilutions, using only the high dilutions at the time of the first test and increasing the concentration of the test material only when these dilutions elicit no reactions.

Finally, it may be well to point out that there is no complete unanimity of opinion as to the value of some of the skin tests listed in table 2. Therefore the data presented had to be based on our own experience and, where such personal experience was lacking or inadequate, on what appeared to be the best available information in the literature.

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CUTANEOUS LEISHMANIASIS

Report of Cases Occurring in Great Britain and the United States

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THE DIAGNOSIS of cutaneous granulomas has been complicated recently by the appearance of patients with cutaneous leishmaniasis, a disease hitherto rarely seen by American dermatologists. One case has been seen in the United States, and five have been discovered in Scotland.

Cutaneous leishmaniasis is an endemic, papuloulcerative disease due to an infestation with a protozoal parasite, Leishmania tropica. The infection is limited to the cutaneous surfaces of the body and is self limited. It is known by various synonyms, some of which are Oriental sore, Biskra button, Delhi boil, Bagdad boil and salek. The last is a term used by the natives of Iran which, interpreted literally, means a "small year." This name has been given to the disease because the lesions tend to heal spontaneously within eight to ten months. The causative organism was first discovered, described and photographed by Borowsky in 1897. It is morphologically similar to Leishmania donovani (kala-azar) and to Leishmania americana (mucocutaneous leishmaniasis). The infection is transmitted by the bite of a sandfly, the Phlebotomus papatasii, or by direct transmission of infected material. An animal reservoir is found in infected dogs and gerbils (jumping mice). It is from this source that the infection is contracted by the sandfly.

HISTOPATHOLOGY

Histopathologically, these infections may be divided into three groups, the follicular or tuberculoid form, the diffuse macrophagic type and the syphiloid form. The tuberculoid form presents characteristic follicles in the superficial layers of the skin. They are formed by a collection of epithelioid and giant cells surrounded by a crown of inflammatory lymphoplasmocytes. The lesions may be differentiated from cutaneous tuberculosis by the presence of large numbers of Leishman-Donovan bodies in the giant and epithelioid cells. However, as the lesions progress the Leishman-Donovan bodies disappear, and when they do so it is

almost impossible to differentiate the lesion from that of lupus vulgaris. The diffuse macrophagic type, which is almost always seen in the beginning of the disease, presents a diffuse infiltrate of macrophages which invade the connective tissue of the cutis. The subepidermal layers present generalized edema, and the macrophages form large areas, the central portions of which are frequently necrotic. The infiltrate is composed of lymphocytes, macrophages, eosinophils, occasional plasma cells and plasmocytes. Giant cells are also found, and their cytoplasm is loaded with Leishman-Donovan bodies. These bodies are also found in the macrophages as well as in the intercellular spaces. The syphiloid type is characterized by follicular formations, typical or atypical, and a lymphoplasmocytic infiltrate, the characteristic elements of which are epithelioid cells, rare macrophages, lymphocytes and plasmocytes. The plasmocytes, connective tissue cells and epithelioid cells are frequently filled with Leishman-Donovan bodies.

CLINICAL APPEARANCES

Clinically the lesions first make their appearance in the form of small erythematous papules covered with reddish brown scale, closely resembling indolent mosquito bites. These lesions appear after an incubation period of two weeks to over one year, the average period being about three to four weeks. One patient seen in 1948 had left Iraq two years previously, and so this time had elapsed since he was in an area endemic for the disease.

Characteristically, the lesions appear on exposed surfaces such as the hands, forearms, face, nose and ears. This predilection can be well understood when one considers the means of transmission. The papules usually cause little or no local discomfort. The lesions then gradually enlarge; the color changes to a dusky reddish purple, and softening of the lesion begins. As this occurs the surface assumes a glazed appearance and the scaling becomes more pronounced. Finally, the lesion becomes surrounded by a narrow zone of chronic infiltration and after three or four months (it is assumed that no local trauma has occurred) ulceration takes place. The resultant ulcer is painless and usually 1 inch (2.5 cm.) or more in diameter. The area is raised and has a hard red edge. If the organisms spread beyond the immediate area there results localized lymphangitis and in rarer cases lymphadenitis may occur. After eight to ten months healing occurs spontaneously leaving a pink or white atrophic scar. One attack usually confers lifelong immunity. Systemic symptoms are rarely, if ever, seen.

Another form of cutaneous leishmaniasis exists which is of extreme interest to dermatologists and which will remain so for the next eight to ten years. This form is the so-called recidival form, or the relapsing lesion. It occurs about the edges of the healed lesions and assumes the

form of small, nonulcerating brownish red tubercles. These lesions are best understood if one considers the manner of their origin. During the course of the acute infection there is a certain amount of migration of parasites into the immediately surrounding tissues. In the patients who acquire the relapsing lesion the degree of immunity established during the healing of the acute infection is insufficient for some reason, such as insufficient therapy or debility on the part of the patient. Hence, these organisms are not destroyed in the healing process, and they may later give rise to the relapsing type of the disease.

DIAGNOSIS

When the diagnosis of cutaneous leishmaniasis is suspected there are three laboratory methods which are useful in verifying the diagnosis. The first consists in examination of scrapings taken from the border of the lesion. These are stained by the Giemsa technic and the slide examined under oil immersion lens. When present the organisms are found to be 2 or 3 microns in diameter. The cytoplasm stains light blue and contains two distinct reddish purple chromatin masses, one large and pale, the trophonucleus, and the other small and deep staining, the blepharoblast. The parasites are found chiefly in the cytoplasm of endothelial cells although they occasionally occur extracellularly or in the cytoplasm of polymorphonuclear leukocytes. They are best demonstrated in preparations obtained from new lesions, where they are quite abundant. As the lesions become older the number of organisms rapidly declines, so that at the end of five or six weeks it is almost impossible to demonstrate the parasites by smear.

In older lesions the best method of identification is found in the use of cultures. Material taken from the edges of the lesion is inoculated into a culture tube containing 5 cc. of Locke's dextrose agar solution to which 0.5 cc. of defibrinated rabbit blood has been added. Incubation is carried out at 24 to 25 C., and growth may not be visible for as long as four weeks. In culture the organism assumes a different appearance from that which it has on smear. It appears as an actively motile, flagellated, trypanosome-like structure. These forms are readily found in the turbid supernatant fluid which forms at the top of the culture tube.

The third aid in diagnosis is the use of a vaccine prepared from L. tropica. The organism is killed by the addition of 0.5 per cent phenol to a saline suspension containing 1,000,000 organisms per cubic centimeter. This material is injected intradermally, and the reaction is read twenty-four and forty-eight hours later, a positive reaction being indicated by erythema and infiltration. A control consisting of 0.5 per cent phenol in saline suspension is used. The latter two methods are particularly useful in diagnosis of the recidival form of the disease.

TYPICAL CASE REPORTS

The following are case reports of 2 patients who were found to have leishmaniasis and who were living in a nonendemic zone.

Fig. 1 (case 1).—Typical erythematous papular lesion of leishmaniasis.

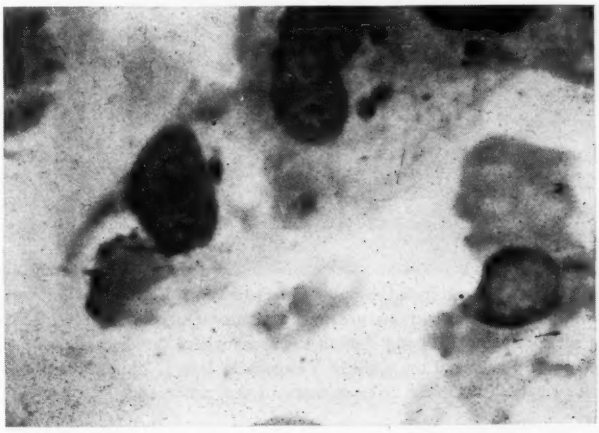

Fig. 2.—Smear from case 1, showing Leishmania tropica.

CASE 1.—J. E. J., a Negro aged 25 years, was seen by one of us (R. C. M.) on Dec. 26, 1945, complaining of a red area on the right cheek, which had been present for about six months. The patient stated that six months previously, while he was in Naples, Italy, a small, indurated papular area had developed on the right cheek. The lesion gradually increased in size. Examination revealed a granulomatous, indurated, reddish, elevated patch about the size of a 50 cent piece.

A smear from the lesion revealed the presence of leishmania. Treatment was begun on December 29, with injections of stibophen (fuadin®) on alternate days and three exposures of roentgen rays (100 r, no filtration). The patient was last seen on March 29, 1946, and at that time the lesion was completely healed.

Case 2.—A. B., a farm worker aged 40 years, in November 1945 felt a swelling inside his left nostril and was referred by his physician for diagnosis to the ear, nose and throat department of the Royal Infirmary, Edinburgh. Examination revealed an ulcerated, granulomatous mass just inside the left nostril and solid edema of the upper lip. Serologic examination revealed no evidence of syphilis, and a portion of the lesion was removed for histologic examination. This showed, according to the pathologist, a typical picture of tuberculosis cutis. The biopsy was repeated, and a similar report was returned. The patient was then referred to the skin department as having a case of tuberculosis cutis and was seen there

Fig. 3.—Tuberculoid type lesion occurring on the nose.

by one of us (G. A. G. P.), who was able to make a diagnosis of cutaneous leishmaniasis. This was confirmed by the observation of Leishman-Donovan bodies in both of the histologic sections previously taken. Questioning revealed that the man had served during 1944 and 1945 in the areas where the disease was endemic—Iraq, Catania in Sicily and the plain of Vesuvius in Italy. Three doses of roentgen rays (150 r) caused complete disappearance of the tumor and the edema.

To point out further how these lesions may be mistaken for other clinical entities, 2 additional cases are reported which occurred while the patients were in military service.

Case 3.—F. P., aged 23 years, leading aircraftsman, was attached to a meteorologic station in Biskra, North Africa. In October 1943 a red spot appeared on the back and gradually spread as a flat plaque until it reached 3 inches (7.5 cm.) in diameter. Later, other similar red patches appeared on the back of his left hand, in the left jaw area and on the dorsum of his right foot. As the con-

dition refused to heal with various applications, the patient was referred after six months to a military hospital in Naples. Examination showed three yellowish red, discoid plaques, slightly indurated on the areas mentioned. Inspection by diascopy revealed lesions not unlike the "apple jelly" nodules of lupus vulgaris. Microscopic examination revealed Leishman-Donovan bodies. The areas were infiltrated with a solution of berberine sulfate and healed completely within six weeks.

Case 4.—A. K., aged 32 years, was admitted to a military hospital in June 1944 with an ulcer below the right eye and was immediately transferred to the venereology department with a diagnosis of primary syphilis. A thorough exam-

Fig. 4.—Tuberculoid type lesion on the left jaw.

ination revealed no evidence of spirochetal infection, and so the patient was sent to the surgical wards, where the disease was considered to be a rodent ulcer. Histologic sections were compatible with a diagnosis of lupus vulgaris, but this did not seem possible with such pronounced granulomatous ulceration. Eventually the patient was moved to a base hospital in Naples with the diagnosis of rodent ulcer. When examined by one of us (G. A. G. P.) he was found to have a large dirty ulcer below the right eye, with edema of both eyelids and the cheek. The ulcer was situated on an indurated base with sloping edges, the surrounding skin being purplish brown. A smear revealed Leishman-Donovan bodies. The response to roentgen rays (150 r, three doses at fortnight intervals) was excellent, the edema vanishing and only slight scarring remaining.

TREATMENT

The treatment of cutaneous leishmaniasis falls into two categories, the choice depending on the number of lesions present and on their anatomic location. First let us consider the treatment of cases in which there are less than six lesions. Here there are five therapeutic methods available, all of which are quite satisfactory. The first consists in the use of a 1 per cent solution of berberine sulfate injected intradermally about the borders of the lesion. Authorities have stated that the dose administered at any one time should not exceed 2 cc. because of toxic reactions. However, we have in a few cases given as much as 5 cc. without reaction. The chief objection to this method of treatment is the intense burning sensation that accompanies the injection. In order to remove this objection we first tried infiltrating the area with a 1 per cent solution of a procaine hydrochloride prior to treatment and later found that the berberine sulfate could be prepared in a solution of procaine, the number of operations thus being reduced from two to one. This method proved very satisfactory in our hands and was particularly adapted to treatment in dispensaries where no x-ray facilities were available. Berberine sulfate seems to be highly effective in cases from Iraq, Iran, and India but useless in those contracted in North Africa or Italy. Roentgen rays were particularly effective in the latter type. The second method available but which was used by no one of us consists in the application of a 20 per cent solution of vegetable charcoal in concentrated nitric acid. This is applied once every seven days until the lesion has disappeared. We learned of this method from Professor S. Adler of Jerusalem, and he assured us that the scarring that results is negligible.

The next two methods of treatment are destructive and quite obviously should not be used on the face or in other areas where obvious scarring should be avoided. The first involves the use of solid carbon dioxide in cauterizing doses. Usually one application is sufficient to destroy the lesion, but occasionally a second or third application is needed. The other is the use of actual hot cautery. The last of the measures to be discussed under this category and the most satisfactory consists in the use of roentgen radiation. This has the obvious advantages of being painless and producing the best cosmetic result. It is quite certain that the roentgen rays do not cause death of the organisms by a direct effect since it has been stated by authorities that 2×10^6 erythema dose of roentgen radiation is required to cause death of the organisms in vitro. Therefore, we must assume that the roentgen rays produce some change in the tissues which enables the tissues of the host to overcome the parasites.

In patients having more than six lesions it was found that use of these local measures was time consuming, and, when one dealt with large numbers of patients, as it was necessary to do in military service,

a method of treatment was sought whereby systemic therapy might produce the same results. At that time a pentavalent antimony compound, stibamine glucoside, a nitrogen glucoside of sodium *p*-aminophenylstibonate (neostam®) was recommended, but, because of the severe reactions following its use, we turned to a trivalent antimony preparation, stibophen, sodium antimony III biscatechol-2,4 disulfonate heptahydrate, sold under the trade name of fuadin.® Stibamine glucoside was recommended in doses up to 0.3 Gm. given intravenously, but our experience showed that 3 out of 4 patients who received 0.1 Gm. experienced nausea and cramps and had projectile vomiting. Used locally in a manner similar to that employed with berberine sulfate the drug seems to be quite effective. Stibophen, however, was given intramuscularly in doses of 5 cc. every five to seven days, and only one reaction to the drug was experienced. This was mild and consisted only of an aching of the larger joints. Retrogression of the lesions usually begins during the latter part of the second week and is usually complete by the end of the fifth or sixth week.

SUMMARY

Four cases of cutaneous leishmaniasis are reported, 2 of them chosen from 6 occurring in civilian practice in nonendemic areas. A recidival form of the disease is discussed, with emphasis placed on the possibility of these lesions appearing in previously infected persons. The methods of treatment and diagnosis are reviewed.

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MULTIPLE SIMULTANEOUS ANOMALIES OF THE HAIR

Report of a Case Exhibiting Trichorrhexis Nodosa, Pili Annulati and Trichostasis Spinulosa

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SOME ANOMALIES of the extruded portions of hair shafts are not easily recognized. Abnormalities of hair development and growth are in general not too well understood. For these reasons and because most hair conditions of the kinds herein described are of minor fundamental importance, they are rather infrequently reported. However, the simultaneous occurrence of three distinct abnormalities of the hair in the same patient is odd enough to warrant reporting. In addition, some clinical observations and certain anamnestic data of this case merit discussion because they are etiologically suggestive and otherwise interesting.

Fig. 1.—Pili annulati.

REPORT OF CASE

N. T., a housewife aged 39 years, complained of a brittleness of the scalp hair of six months' duration which had resulted in the appearance of her having a very poorly designed and unkempt crew cut. This was said to be the third episode of the same condition. The first one had occurred about 30 years ago (at age 9) in conjunction with an attack of influenza (epidemic of 1917). At that time the hair of the head had become irregularly short and remained so for about six months, after which there had been gradual spontaneous restoration to normal. A second time had been 17 years ago (at age 22), after a long illness diagnosed as pleurisy. On this occasion the cropped appearance persisted for about a year before the usual character of the hair reasserted itself. The present episode had begun after the birth of twins from an apparently uneventful pregnancy. Another pregnancy six years before, which had resulted in a single child, had not been attended by any such trouble. Parenthetically it may be noted at this point that this child, a girl, has ringed hairs which are of average length.

Gross examination of the patient's scalp hairs showed them to be of three varieties. The most abundant were brownish, coarse and very short (1 to 2

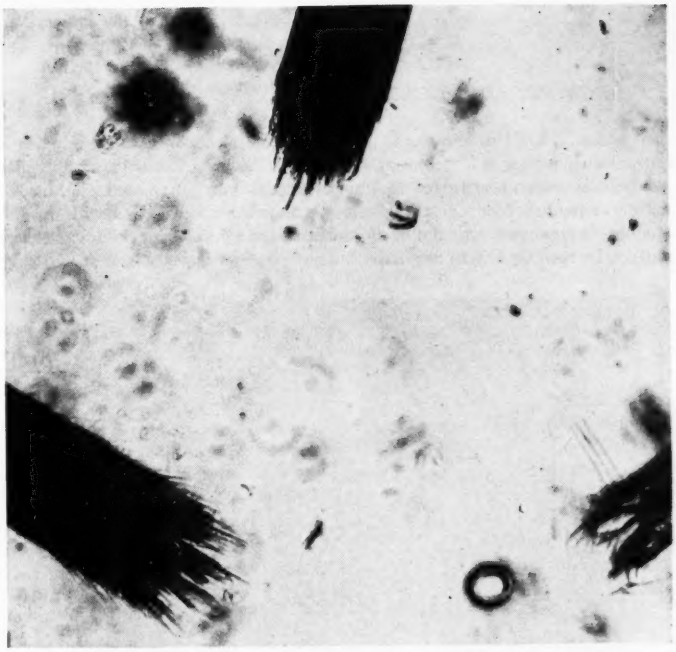

Fig. 2.—Trichorrhexis nodosa. Appearance at point of complete fracture.

Fig. 3.—Trichorrhexis nodosa. Appearance at a point at which an acute-angled bend was made.

inches [2.5 to 5 cm.] in the main). The next most numerous were grayish, fine and somewhat longer (2 to 3 inches [5 to 7.5 cm.]). These hairs by reflected light could be seen to be ringed in a spiral fashion but not twisted. A third kind of hair was reddish (copper colored), longer than the others (3 to 4 inches [7.5 to 9.0 cm.]), least numerous and most normal looking. Nodosities or beadedness could not be seen or felt in any hairs. The eyebrows appeared short and ragged.

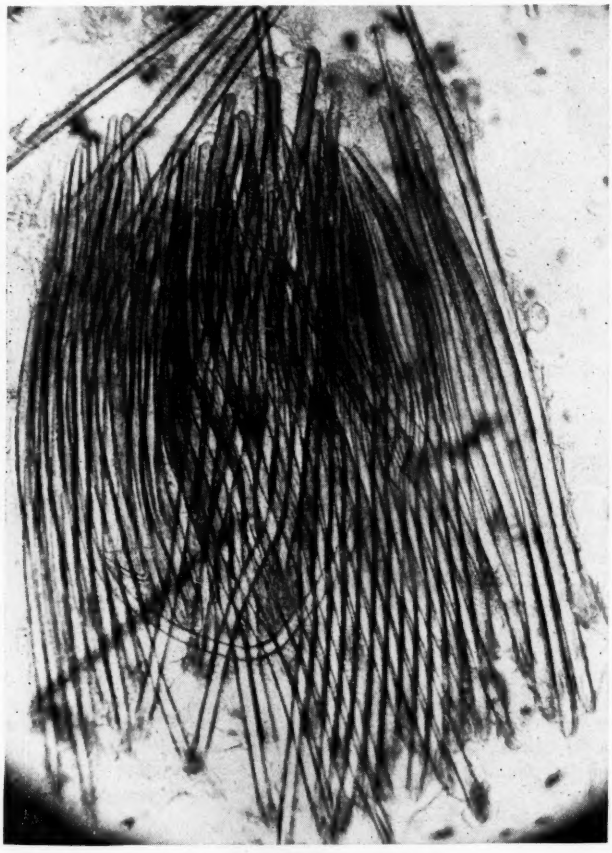

Fig. 4.—Trichostasis spinulosa.

On the brow and on the tip and wings of the nose the pilosebaceous orifices seemed plugged with comedo-like structures which, however, had fuzzier surfaces than comedos ordinarily show. The axillary and pubic hair looked normal.

Microscopic examination ot the scalp hairs revealed two phenomena. There were dark central spots in the medullary position (fig. 1) or dark peripheral streaks in the cortical zone alternating with lighter areas, and this picture was to be seen more extensively in the gray hairs but to some extent in the brown.

Then there were dovetailed, brush fractures (figs. 2 and 3) frequently seen in the brown hairs and occasionally in the gray ones. The reddish hairs appeared normal. To correlate these observations with the clinical appearance, the gray hairs contributed most to the gross ringed impression and the greater number of shredded fractures in the more abundant brown hair contributed most to the ragged, cropped condition. The sum of all of these effects produced the patient's unsightly coiffure.

Extraction and examination of some of the comedo-like structures from the nose and brow showed them to be tiny bundles of hair containing numbers of lanugo filaments surrounded and enmeshed in a sheath of amorphous debris (fig. 4).

Treatment consisted of the application of ointments and lotions containing combinations of salicylic acid, mercury or sulfur and resorcinol, the administration of thyroid substance by mouth, ultraviolet irradiation and mechanical protection of the hair. Suggestions were made for the avoidance or minimizing of traumatizing manipulations in washing and combing. The constant wearing of a snug skull cap was advised to protect particularly against movements of the head on pillows during sleep. Within a period of observation covering six months, the hair grew to a length which permitted an acceptable boyish tonsure. At nine months more elaborate forms of feminine hair-do requiring longer hair and curling could be maintained.

COMMENTS

In general textbooks of dermatology, accounts of anomalies of the hair of these types are meager, repetitive of data from few and ancient cases and subtly reflective of the relative unimportance of the subject. Therefore new or corrected ideas and observations should be of some interest.

Trichostasis spinulosa is stated to be rare. What is accounted rare or common depends in a measure on what is the statistical frame of reference and with what diligence a condition is sought. As the result of observation of this case plus many others that I have noted in routine examinations of the skin and its appendages for other conditions, I should call trichostasis spinulosa common in the sense that, if sought for, it can be discovered in one's general dermatologic material several times yearly.

Pili annulati, or ringed hair, and trichorrhexis nodosa, again with the aforementioned statistical frame of reference, are indeed rare conditions. With regard to ringed hair, its presence in this patient and in a daughter suggests that it is a gene-determined anomaly.

With regard to trichorrhexis nodosa, several more things can be said. The repeated episodes of the condition in this patient, their periodicity related to severe constitutional debility or strain and eventual spontaneous restitution to integrity each time suggest that trichorrhexis nodosa is the result of metabolic disturbance. One may imagine that under circumstances of considerable physical depletion, such as may occur in influenza, pleurisy and twinning, less important structures of the body like hair and nails and less important items in the body

economy like their growth and function may very well be deprived of whatever they require for average development. Onychomadesis, Beau's lines, various grades of toxic defluvium and less startling changes of the character of the hair following severe illness are common and well known sequelae. Trichorrhexis nodosa may be just another type, rather uncommon, of this sort of disorder.

One observation was made which I have not seen described or emphasized elsewhere. It was found that in those hairs which already showed the characteristic bushed fracture of trichorrhexis nodosa, any number of new fractures could be produced at will by sharply bending the shaft of the hair at any point. Examination under the microscope of the angled sites revealed a hair with as many points of typical fragmentation into filaments with greenstick or complete rupture and brush dovetailing as bends made. This observation suggests that the potentiality to fracture is present all along the shafts of such metabolically disturbed hairs and not at particular points only. Then it would seem that the trauma of washing, combing and setting of the hair and movements of the head on pillows determine at what lengths, where and how often hairs are broken off. And, if this is true, the most valuable part of treatment is mechanical protection of the hair from injury of all sorts until the underlying metabolic causes abate or disappear.

There is one final point to be made. Some observers are reported to be of the opinion that external and local factors alone like aging, drying and harsh manipulation of hair are the sole causes of trichorrhexis nodosa. They are said to have found the condition in well used objects made of animal hairs, like shaving brushes. It happened that when I received this case I had an old and honored shaving brush which was ready for retirement from active service. It had served me for some ten years, and I calculate that it partook in the lathering ritual about 3,500 times. The bristles were worn to perhaps half their original length. Examination of these hairs under the microscope revealed them to be finely tapered and occasionally separated in the long direction into two, rarely more than two, still finer strands (trichoptilosis). Never was the typical bushed fracture of trichorrhexis nodosa found. Is it possible that those who found the condition in their old shaving brushes were unfortunate in that they had secured brushes made from the hairs of lately sick badgers that had developed in their hair the potential for trichorrhexis nodosa? The condition, identical with the human form, occurs in animals.[1]

820 Caton Avenue (18).

1. Henry, A., and Bory, L., in Darier, J., and others: Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936, vol. 7, p. 865.

SQUAMOUS CELL CARCINOMA SIMULATING GRANULOMA INGUINALE

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SQUAMOUS cell carcinoma and granuloma inguinale at times resemble each other so closely that differentiation on clinical grounds alone may be impossible. Speiser [1] and Pund and Greenblatt [2] reported 4 and 2 cases, respectively, of granuloma inguinale of the cervix which were diagnosed clinically as carcinoma. Philpott [3] reported a case of granuloma inguinale of the penis which simulated carcinoma, the correct diagnosis not being established until Donovan bodies were demonstrated in the depths of the tissue when the granulomatous mass was excised. Chen, Greenblatt and Dienst,[4] in a series of 95 referred patients in whom the disease had been diagnosed as granuloma inguinale, found that 6 (6.3 per cent) actually had squamous cell carcinoma. Moore [5] reported a case which was clinically diagnosed as carcinoma of the penis and which was not proved to be granuloma inguinale until, after many biopsies, Donovan bodies were found. It is imperative, in view of therapy and prognosis, that these conditions be correctly differentiated. The recent observation of 3 cases of carcinoma which were diagnosed and treated as granuloma inguinale, with death resulting in 2, prompted

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1. Speiser, M. D.: Four Cases of Granuloma Inguinale of Cervix Diagnosed Clinically as Carcinoma, Am. J. Obst. & Gynec. **56**:1181 (Dec.) 1948.

2. Pund, E. R., and Greenblatt, R. B.: Granuloma Venereum of Cervix Uteri (Granuloma Inguinale) Simulating Carcinoma, J. A. M. A. **108**:1401 (April 24) 1937.

3. Philpott, O. S.: Pseudoepitheliomatous Hyperplasia Due to Granuloma Inguinale, Arch. Dermat. & Syph. **56**:669 (Nov.) 1947.

4. Chen, C. H.; Greenblatt, R. B., and Dienst, R. B.: Recent Observations on Granuloma Inguinale, with Report on Streptomycin Therapy, Arch. Dermat. & Syph. **58**:703 (Dec.) 1948.

5. Moore, M.: Granuloma Venereum Simulating Carcinoma: Report of a Case with Diagnostic and Therapeutic Complications, Arch. Path. **45**:787 (June) 1948.

the writing of this paper. It is presented with the hope that with the stimulation of thought concerning this matter similar errors by others may be prevented.

REPORT OF CASES

CASE 1.—B. B., a 47 year old Negro woman, was admitted to Bellevue Hospital on Dec. 26, 1946, for lesions of the vulva of six months' duration. She had received intramuscular injections twice weekly for seven weeks from her private physician who referred her for hospitalization with the diagnosis of granuloma inguinale.

Examination on admission showed multiple granlomatous, ulcerative lesions of the left genitocrural fold, left labium majus, right labium minus and pubic area;

Fig. 1.—Granulomatous, proliferative tumor involving the pubic area, vulva, thighs and left buttock (case 1).

the diagnosis of granuloma inguinale was made. Serologic tests for syphilis gave negative reactions. The erythrocyte count and hemoglobin were 3,300,000 and 10.0 Gm., respectively. On December 27 a stained smear of tissue scraped from the lesion was reported to contain Donovan bodies. Accordingly, a course of stibophen (fuadin,® a trivalent antimony compound) was started on the same day, 5 cc. being given intramuscularly daily for one month; no improvement was noted. From Feb. 19 to March 30, 1947, the patient received 0.5 Gm. of streptomycin daily, for a total dose of 19.5 Gm. No benefit was observed.

By June 28, 1947, on which date a biopsy was done, the proliferative, granulomatous tumor had spread to involve a considerably larger area (fig. 1), the

erythrocyte count and hemoglobin had fallen to 2,750,000 and 5.75 Gm., respectively, and the patient's general condition was much worse. The biopsy section (fig. 2) showed irregular masses and cords of atypical, pleomorphic squamous cells growing down from one area of intact epidermis; a mild chronic inflammatory infiltrate was present, but the characteristic large mononuclear cells, Donovan bodies and plasma cells were not observed. The histopathologic diagnosis was squamous cell carcinoma, with no evidence of granuloma inguinale. Subsequently, repeated tissue scrapings were stained and examined for Donovan bodies; none were found.

The malignant growth was considered too far advanced for therapy, and so the patient was transferred to a home for incurables, where she died on Dec. 23,

Fig 2.—Photomicrograph showing masses and cords of atypical pleomorphic squamous cells in biopsy section of case 1 (hematoxylin and eosin; × 163).

1947, one year from the date of admission to Bellevue Hospital and approximately eighteen months from the start of her illness.

Case 2.—L. C., a 37 year old Negro woman, was admitted to Bellevue Hospital on Sept. 18, 1946. One year previously she had noted the development of edema of the right labium majus and ulceration of similarly placed lesions which elsewhere had been called venereal warts. Treatment with sulfathiazole and later antimony potassium tartrate (tartar emetic) was instituted by her physician, but the ulcerated area continued to enlarge. During the three months prior to admission she was treated with stibophen at another institution and on failure to improve was transferred to Bellevue Hospital with the diagnosis of granuloma inguinale.

Examination on admission showed an edematous, ulcerated, granulomatous mass, covered with a greenish, purulent exudate, involving the vulva, particularly on the right side. The admitting physician made a diagnosis of granuloma inguinale but stated that carcinoma should be considered. Serologic tests for syphilis gave negative reactions. An erythrocyte count and hemoglobin were 3,400,000 and 9.0 Gm., respectively. On the following day, a stained piece of tissue from the lesion was reported to contain Donovan bodies.

Treatment with stibophen was started in a dosage of 5 cc. intramuscularly three times weekly and was later increased to 5 cc. daily; little improvement could be observed. On October 11 radiation therapy was begun: 150 r at 200 kilovolts, 20 milliamperes and with filtration of 0.5 mm. of copper and 1.0 mm. of aluminum was delivered every two or three days for a total of nine exposures. Following this

Fig. 3.—Tumor involving the vulva and adjacent areas (case 2).

treatment there was definite improvement. One month later a similar course of therapy was given. On February 17 streptomycin became available, and the patient received 0.5 Gm. daily for thirty-three days with no apparent benefit.

Despite the stibophen, radiation, transfusions of whole blood, protein hydrolysates, vitamins, iron, penicillin and streptomycin given the patient, she steadily failed in health. Pronounced weakness, diarrhea and considerable bleeding from the tumor developed, with a fall of the erythrocyte count and hemoglobin to 2,180,000 and 6.5 Gm., respectively. Erosion through the rectovaginal wall, producing a fistula, necessitated a loop colostomy. By July the tumor had spread to involve a large area (fig. 3). At this time two discrete, firm nodes were noted in the inguinal region and a biopsy of a specimen from the granulomatous mass was done. The section showed a mass of tumor tissue consisting of cords and nests of anaplastic, infiltrating, pleomorphic tumor cells (figs. 4 and 5). In a few places there was direct connection of the tumor with the epidermis. The cells were for the most part large, with large basophilic nuclei. Keratinization of nests of tumor cells was

observed. The tumor had infiltrated all the subcutaneous tissue. A lymphocytic infiltrate was present, but plasma cells, large mononuclear cells and Donovan bodies were not seen. The histopathologic diagnosis was squamous cell carcinoma, with no evidence of granuloma inguinale. Subsequent attempts to demonstrate Donovan bodies in stained smears of tissue scrapings were unsuccessful.

The patient died on Aug. 25, 1947, eleven months after admission to the hospital and approximately two years from the onset of her illness.

CASE 3.—J. T., a 40 year old Negro, was admitted to Bellevue Hospital on June 20, 1949. The history he gave concerning his illness was in part confirmed

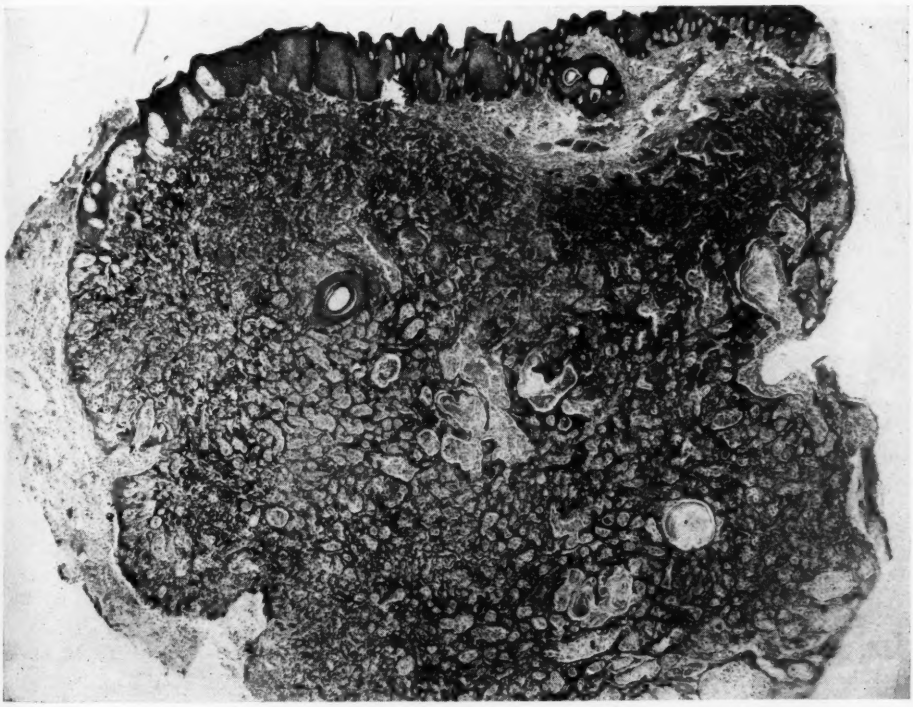

Fig. 4.—Low power view of section from case 2 showing extensive infiltration of the corium and subcutaneous tissue by tumor cells growing down from the epidermis (hematoxylin and eosin).

and in part contradicted by information obtained from other institutions at which he had been treated. The communications received from these other hospitals were themselves, in some cases, incomplete or confused. Apparently the patient had been well until 1937, when a lesion, diagnosed as a chancre, appeared on the tip of the prepuce. At that time two lesions were also observed on the glans penis and the patient was informed that these were venereal warts. Intermittent antisyphilitic therapy was received for several years. In 1942 the patient was hospitalized

because of elephantiasis of the prepuce of three months' duration and an ulcer between the base of the penis and scrotum. A plastic repair was done, after which the patient left the hospital against advice. According to his story the penis did not completely heal. However, in a communication from another institution where he received treatment for gonorrhea in 1943, it was stated that no penile lesions were observed at that time. In March 1948 he was again hospitalized because of penile lesions. A diagnosis of granuloma inguinale was made, although a biopsy showed only chronic inflammation with no Donovan bodies. The patient received 70 injections of streptomycin, in a dosage of 0.5 Gm., over a two week period. One month later not only were the original lesions unchanged but also new

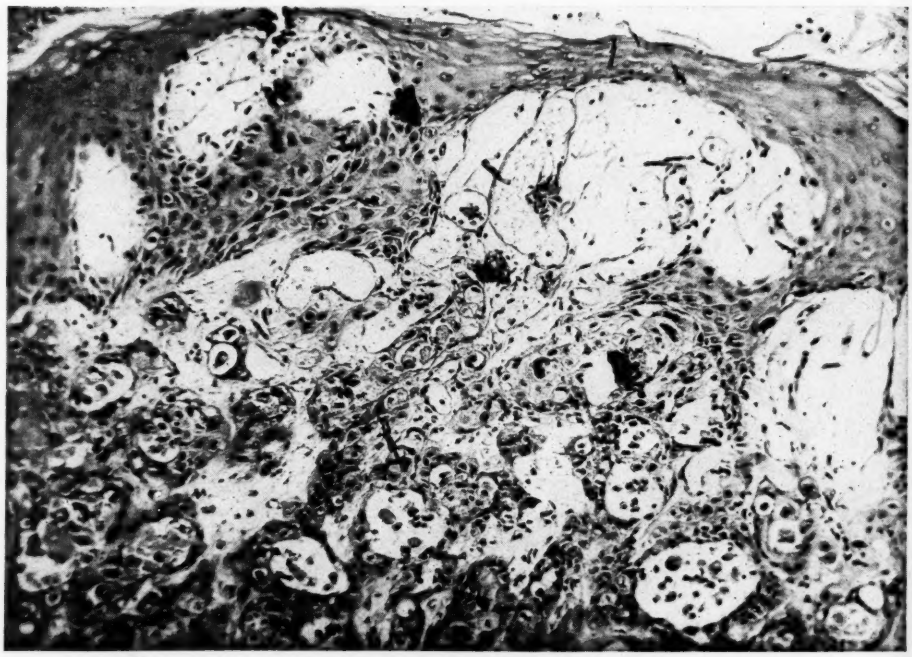

Fig. 5.—High power view of the same section as in figure 4 showing the anaplastic, pleomorphic nature of the tumor cells (hematoxylin and eosin; × 163).

ones had appeared in the pubic area. A second and third course of streptomycin were also ineffective in stopping progression of the disease, as was a course of aureomycin. The patient was transferred to Bellevue Hospital with the diagnosis of "chronic granuloma inguinale."

Examination on admission showed an emaciated person with a destructive, ulcerative, granulomatous process, bathed by a greenish yellow exudate, involving the penis, scrotum and pubic and left inguinal areas (fig. 6). Considerable destruction of the penis was evident, only the tip of the glans having been spared. A thick, cordlike band of depigmented tissue extended around the periphery of the ulcerated area. Scars on the thighs marked the donor sites for the previous grafts.

Fig. 6.—Destructive granulomatous tumor involving the genitalia and pubic and left inguinal areas (case 3). Of the penis, only the tip of the glans has not been destroyed.

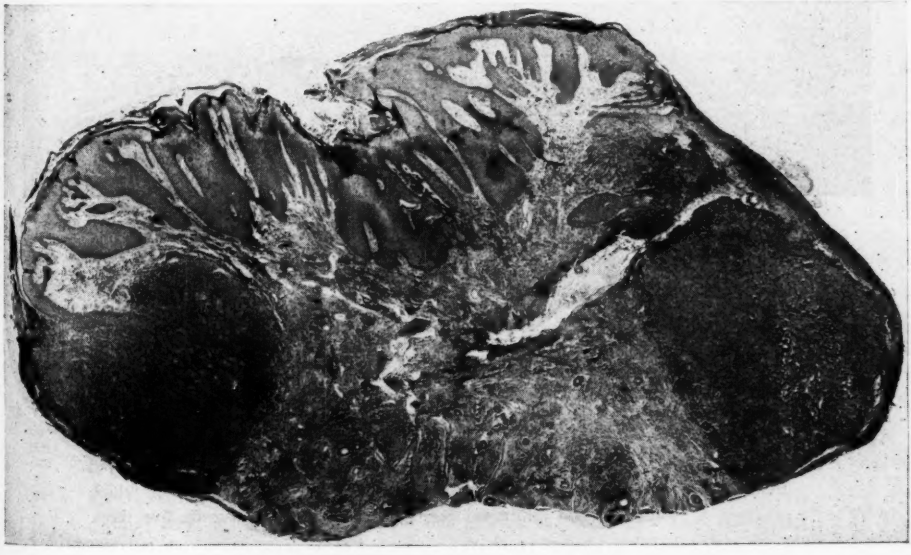

Fig. 7.—Low power view of biopsy section from case 3 showing a mass of tumor cells at each end (hematoxylin and eosin).

A diagnosis of granuloma inguinale was made by the admitting physician. However, when I saw the patient the following day the striking resemblance to cases 1 and 2 led me to the clinical diagnosis of squamous cell carcinoma. Serologic tests for syphilis gave negative reactions. The erythrocyte count and hemoglobin were 2,610,000 and 8.5 Gm., respectively. On June 23 two pieces of tissue were excised for histologic examination. At the same time material was removed from the depths of the lesion and after staining was searched for Donovan bodies; no such organisms were found. The tissue excised from the border showed fibrous tissue proliferation with a moderate perivascular infiltrate consisting chiefly of

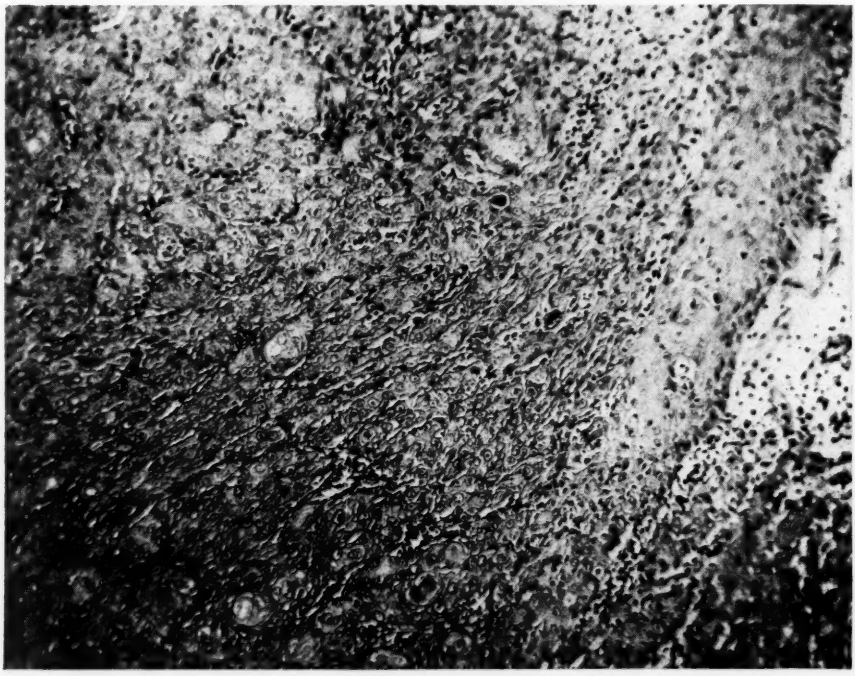

Fig. 8.—High power view of the same section as in figure 7 showing anaplastic tumor cells arising from a rete peg on the left (hematoxylin and eosin; × 144).

plasma cells and lymphocytes. The section from the center of the involved area showed a decidedly acanthotic epidermis with areas of ulceration at either end. The tumor cells, which varied considerably in size, shape and staining properties, were present in large sheets (figs. 7 and 8). Connection of the malignant cells to the overlying epidermis was observed. Large mononuclear cells and Donovan bodies were not seen. The histopathologic diagnosis was squamous cell carcinoma, with no evidence of granuloma inguinale.

The diagnosis of malignancy being established, radiation therapy was started without delay. The involved area was divided into three parts, each of which was given a total of 30,000 milligram hours over a period of twenty-five days.

A 5 Gm. radium pack at a distance of 6 cm. with filtration of 2.5 mm. of platinum was employed. This treatment was followed by almost complete healing. When last seen, in October 1949, the patient had undergone the first of a series of plastic operations designed to replace the scar tissue.

COMMENTS

Numerous reports have appeared concerning the development of carcinoma in lesions of such chronic conditions as acrodermatitis chronica atrophicans, nevus unius lateris, Darier's disease, leprosy, psoriasis, condyloma acuminatum, scars from thermal burns, varicose ulcers, syphilis, lupus erythematosus and fistulas of osteomyelitis, lymphogranuloma venereum and tuberculosis. Prior to the utilization of streptomycin, granuloma inguinale frequently persisted for years despite treatment. Therefore it was surprising that a review of the literature disclosed only 3 cases in which the disease was associated with carcinoma. The first, reported by Cardwell and Pund,[6] was that of a 58 year old Negro woman with a destructive lesion of the cervix, biopsy of which showed a squamous cell carcinoma; in addition, large cells containing Donovan bodies were observed in some areas. On the basis of the history of a whitish vaginal discharge present more than two years prior to the onset of her recent illness, it was suggested that the malignant growth was secondary to granuloma inguinale. The validity of such reasoning may be questioned. The second case, in which granuloma inguinale was again associated with an epithelioma of the cervix, was merely mentioned in a report by Pund, Greenblatt and Huie.[7] Since the last mentioned paper was based on case histories in the files of the University of Georgia School of Medicine and since the patient described by Cardwell and Pund was studied at the same institution, it is not unlikely that both reports were of the same patient. The third case [8] was that of a 50 year old Negro with a penile lesion containing Donovan bodies. Biopsy showed only the picture of granuloma inguinale. However, biopsy specimens taken twenty-three days after the start of therapy with antimony potassium tartrate showed squamous cell carcinoma.

In view of the infrequency with which granuloma inguinale has been found associated with carcinoma, the observation of 3 such cases at one hospital within a short period is unusual. However, careful analysis

6. Cardwell, E. S., Jr., and Pund, E. R.: Development of Carcinoma Secondary to Venereal Lymphogranuloma and Granuloma, and Carcinoma, J. M. A. Georgia **29**:60 (Feb.) 1940.

7. Pund, E. R.; Greenblatt, R. B., and Huie, G. B.: The Role of the Biopsy in Diagnosis of Venereal Granuloma and Lymphogranuloma and Chancroid, Am. J. Syph., Gonor., & Ven. Dis. **22**:495 (July) 1938.

8. Lynch, K. M.: Granuloma Inguinale, J. A. M. A. **77**:925 (Sept. 17) 1921.

leads to considerable doubt as to the existence of the former disease in the patients on whom the present report is based.

The demonstration of what were believed to be Donovan bodies in cases 1 and 2 gave laboratory support to the clinical impression of granuloma inguinale. However, examination of a stained tissue smear is a difficult procedure, and considerable experience is required, not only to find the organisms, but also to distinguish true Donovan bodies from artefacts. Since the examinations were performed by persons relatively inexperienced in this procedure there are grounds for reasonable doubt as to the validity of the laboratory report of the observation of Donovan bodies in cases 1 and 2. This doubt is increased by the failure to find these organisms on subsequent attempts. Donovan bodies, to my knowledge, were never demonstrated in case 3, the diagnosis of granuloma inguinale having been made purely on clinical grounds.

As pointed out by Pund and Greenblatt,[2] the essential histopathologic feature of granuloma inguinale is the exuberant granulation tissue, containing numerous plasma cells and polymorphonuclear leukocytes, in which the pathognomonic large mononuclear cells containing Donovan bodies are found. In none of the 3 cases did biopsy show a histologic picture considered characteristic of granuloma inguinale.

The introduction of streptomycin made granuloma inguinale, which was formerly therapeutically discouraging, a disease which could be approached with optimism. Numerous reports have confirmed the efficacy of the drug. Nevertheless, it failed to produce significant improvement in these 3 cases. Although patients 1 and 2 received a daily dose lower than what is commonly employed today, Chen, Greenblatt and Dienst,[4] using approximately the same dosage schedule, obtained a cure in 75 per cent of their series, with recurrence in 19 per cent and failure in only 6 per cent. The third patient received three courses of streptomycin, in adequate dosage, without appreciable improvement. In addition, he also failed to benefit from aureomycin, reportedly of value in the treatment of granuloma inguinale.[9]

CONCLUSIONS

One concludes that in these 3 cases the diagnosis of granuloma inguinale was in all probability erroneous and that each patient had carcinoma from the start. This observation emphasizes the necessity of biopsy in every case diagnosed as granuloma inguinale which persists despite adequate therapy. With such effective agents as streptomycin, aureomycin and the most recent addition to our armamentarium, chlor-

9. Dienst, R. B.; Chen, C. H., and Greenblatt, R. B.: Granuloma Inguinale, Urol. & Cutan. Rev. **53**:537 (Sept.) 1949.

amphenicol (chloromycetin®),[10] failure to achieve cure must cast serious doubt on the validity of the diagnosis. Even when Donovan bodies have been reported present, lack of response to therapy demands a biopsy, for the inability to distinguish artefacts may be the cause of error.

SUMMARY

Three cases are reported in which squamous cell carcinoma was originally diagnosed as and treated as granuloma inguinale. Analysis of these leads to the belief that in all the carcinoma was primary, the diagnoses of granuloma inguinale having been erroneous.

The importance of early biopsy in every case diagnosed as granuloma inguinale which fails to respond to adequate antibiotic therapy is stressed.

247 Waterman Street (6).

10. Greenblatt, R. B.; Wammock, V. S.; Dienst, R. B., and West, R. M.: Chloromycetin in the Therapy of Granuloma Inguinale, J. M. A. Georgia **38**:206 (May) 1949.

PODOPHYLLIN IN THE TREATMENT OF CUTANEOUS CARCINOMA

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AND
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PODOPHYLLIN (resin of podophyllum N.F.), an extract of the dried rhizome and roots of the May apple, or mandrake, has been employed for more than one hundred years as a laxative and more recently as a supposed liver stimulant. In 1942, Kaplan [1] reported successful results in the treatment of condyloma acuminatum with topical application of a 25 per cent suspension of podophyllin in liquid petrolatum.

The rapid involution of the condylomas was assumed by Culp and Kaplan [2] to be due to spasm of the small vessels induced by the irritant action of the drug, with resultant ischemia and necrosis. However, the histologic studies of treated lesions by Sullivan and King [3] suggested a different mode of action. They found that 24 to 48 hours after application of podophyllin the epidermis showed two types of change: superficially there was loss of intercellular bridges with accentuation of cell membranes, while in the basal layer and first few rows of the prickle cell layer there were enlarged cells with chromatin material arranged so as to suggest distorted mitosis. These large, abnormal cells, termed "podophyllin cells," were similar to the so-called colchicine figures. It was concluded that the response of condyloma acuminatum is due to podophyllin's "profound and subtle action on cell metabolism."

From the Department of Dermatology, dermatologist in chief, Dr. Francesco Ronchese; Department of Pathology, director, Dr. Herbert Fanger, and Tumor Clinic of the Rhode Island Hospital.

1. Kaplan, I. W.: Condylomata Acuminata, New Orleans M. & S. J. **94**:338 (Feb.) 1942.

2. Culp, O. S., and Kaplan, I. W.: Condylomata Acuminata: 200 Cases Treated with Podophyllin, Ann. Surg. **120**:251 (Aug.) 1944.

3. Sullivan, M., and King, L. S.: Effects of Resin of Podophyllum on Normal Skin, Condylomata Acuminata and Verrucae Vulgares, Arch. Dermat. & Syph. **56**:30 (July) 1947. King, L. S., and Sullivan, M.: Effects of Podophyllin and of Colchicine on Normal Skin, on Condyloma Acuminatum and on Verruca Vulgaris: Pathologic Observations, Arch. Path. **43**:374 (April) 1947.

These observations led to investigation of the drug's effect on plants and lower animal forms. Sullivan and Wechsler [4] immersed the young, growing root tips of Allium cepa in a solution of podophyllin and observed interference in the normal mitotic sequence. Cornman [5] demonstrated the retardation of cleavage of eggs of Arbacia and of the starfish when exposed to podophyllin. Goldsmith and Black [6] decapitated Planaria dorotocephala and applied podophyllin to the posterior sections. Considerable retardation in the regeneration of heads of the treated worms as compared to untreated controls was noted.

Similarity between the cytologic effects produced by podophyllin and those produced by colchicine and the known cancerocidal action of the latter [7] suggested utilization of podophyllin in the treatment of malignant growths. Hartwell and Shear [8] found that podophyllin produced severe damage to sarcoma 37 in mice. Ormsbee, Cornman and Berger [9] noted that it exerted a selective action against mouse tumor cells in tissue culture; in vivo studies also showed pronounced damage to mouse tumor cells following its parenteral administration. Belkin [10] compared the growth of implants of sarcoma 180 in a group of albino mice which received injections of podophyllin in sesame oil and in a control group which was given injections of sesame oil alone. It was found that tumor growth in the test animals decreased promptly so that at the end of two weeks the average size in them was approximately $\frac{1}{7}$ that in the controls. In a similar experiment with mouse mammary adenocarcinoma Belkin found that the terminal volume of the treated tumors was about $\frac{2}{3}$ that of the controls. Histologically, both types of tumor after exposure to podophyllin showed extensive necrosis with nuclear changes consisting of diminution in mitoses, pyknosis, karyorrhexis and an arrest of mitosis before the metaphase, resembling the colchicine effect.

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4. Sullivan, B. J., and Wechsler, H. I.: The Cytologic Effects of Podophyllin, Science **105**:433 (April 25) 1947.

5. Cornman, I.: Inhibition of Arbacia Egg Cleavage by Podophyllotoxin and Related Substances, Biol. Bull. **93**:192 (June) 1947; The Effects of Podophyllin on the Maturation and Cleavage of the Starfish Egg, ibid. **93**:214 (June) 1947.

6. Goldsmith, E. D., and Black, H. M.: The Effect of Podophyllin on Regeneration in Planaria, Anat. Rec. **101**:708 (Aug.) 1948.

7. Ludford, R. J.: Colchicine in the Experimental Chemotherapy of Cancer, J. Nat. Cancer Inst. **6**:89 (Oct.) 1945. Seed, L.; Slaughter, D. P., and Limarzi, L. R.: Effect of Colchicine on Human Carcinoma, Surgery **7**:696 (May) 1940.

8. Hartwell, J. L., and Shear, M. J.: Chemotherapy of Cancer: Classes of Compounds Under Investigation and Active Components of Podophyllin, Cancer Research **7**:716 (Nov.) 1947.

9. Ormsbee, R. A.; Cornman, I., and Berger, R. E.: Effect of Podophyllin on Tumor Cells in Tissue Culture, Proc. Soc. Exper. Biol. & Med. **66**:586 (Dec.) 1947.

10. Belkin, M.: Effect of Podophyllin on Transplanted Mouse Tumors, J. Pharmacol. & Exper. Therap. **93**:18 (May) 1948.

With the in vitro and in vivo demonstration of podophyllin's destructive action on mouse tumors, the next step was its trial in the therapy of malignant growths in human beings. Sullivan [11] treated 20 cutaneous carcinomas with multiple local applications of podophyllin and obtained satisfactory results in all but one. His follow-up period varied from one to eight months. He concluded that the results were encouraging but that it was premature to express enthusiasm for the method until the permanency of his cures had been established.

We have recently had the opportunity to treat one basal cell epithelioma and one squamous cell carcinoma with podophyllin. Since

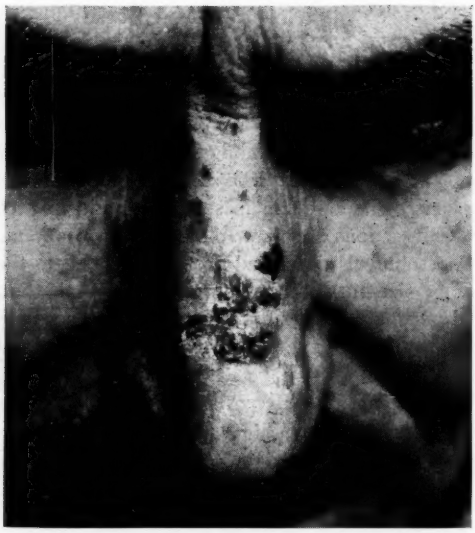

Fig. 1 (case 1).—Basal cell epithelioma prior to therapy.

the proper evaluation of any new technic of therapy requires the pooling of results obtained by different investigators, we believe that a report on our observations may be of value.

REPORT OF CASES

CASE 1.—E. A., a 70 year old white man, was first seen in the dermatology clinic of Rhode Island Hospital on Feb. 8, 1950. At this time he presented a lesion of the dorsum of the nose (fig. 1), measuring 1.5 by 2.5 cm., which had been growing slowly during the preceding three to four years. The affected region showed a large, irregularly outlined ulcer covered by a hemorrhagic crust with an elevated, nodular

11. Sullivan, M.: Treatment of Cutaneous Carcinoma with Podophyllin, Bull. Johns Hopkins Hosp. **85**:200 (Sept.) 1949.

border. Extending from its left inferior pole was an area with intact surface but with an appearance such as to suggest neoplastic change. Slightly superior and to the left of the ulcer was a small crusted area. The diagnosis of basal cell epithelioma was made and was confirmed by biopsy.

On February 10 therapy with podophyllin was started. A 20 per cent solution in 95 per cent alcohol was liberally painted over the affected region as well as a narrow zone of apparently normal skin surrounding it. This procedure was repeated daily, exclusive of week ends, for a total of 15 applications. Shortly after the commencement of therapy a striking change became apparent. The crusts and necrotic material disappeared, with the formation of one large, clean, moderately deep ulcer (fig. 2). After 13 applications this measured 2.5 by 2.5 cm. After completion of this course of treatment on March 6, the patient was seen three times a week and a boric acid ointment dressing applied. Under this regimen the ulcer

Fig. 2 (case 1).—Appearance of the lesion shown in figure 1 on February 17, after five applications of podophyllin. The ulcer subsequently extended peripherally to include the area indicated as *A*, in which regrowth of the tumor was later noted.

gradually began to fill in. However, one week after podophyllin therapy was stopped a small, suspicious knob of tissue was noted at the most inferior pole of the ulcer, in the region indicated as *A* in figure 2. This was excised and the base desiccated. Histologic examination of the removed tissue showed the presence of basal cell epithelioma; no significant cytologic differences between this and the original biopsy could be seen. Treatment with boric acid ointment was continued, and on March 17 the ulcer measured 2.0 by 2.0 cm.; on March 22 it measured 1.3 by 1.7 cm., and on April 7, eight weeks from the start of therapy, it was completely healed (fig. 3). The scar was smooth, slightly depressed, firm and cosmetically satisfactory.

Case 2.—G. M., a 70 year old white man, was first seen in the dermatology clinic of Rhode Island Hospital in November 1948. At this time keratoses on the dorsa of his hands were treated by electrodesiccation. He was next seen on Jan. 27, 1950, when, in addition to several keratoses on the dorsa of hands and fingers, he

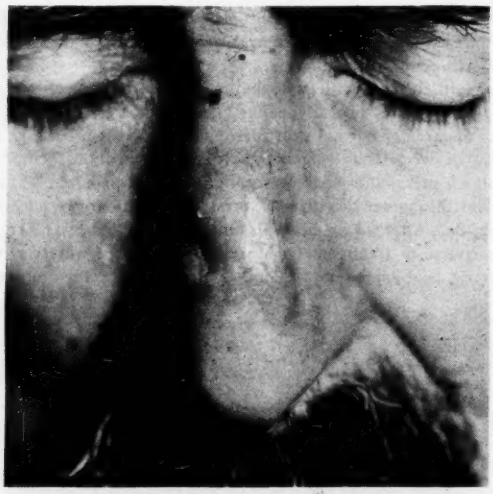

Fig. 3 (case 1).—Appearance of the lesion shown in figures 1 and 2 on April 7, demonstrating complete healing eight weeks after the start of therapy.

Fig. 4 (case 2).—Senile keratoses and squamous cell carcinoma prior to therapy. The right edge of the tumor had been excised for microscopic examination.

presented an elevated, moderately firm, keratotic mass measuring 1.5 by 1.5 cm. on the dorsum of his left hand (fig. 4). Diagnosis of senile keratoses and squamous cell carcinoma were made. Biopsy of the lesion on the left hand showed the structure of squamous cell carcinoma.

Treatment of all lesions with podophyllin was started on January 30, the same procedure being followed as in case 1 except that the drug was applied 18 times. After nine applications the keratoses were unchanged; therefore, their tops were curetted off and therapy was continued as before. However, the hard surfaces reformed, and at the completion of treatment the keratoses were essentially the same as prior to its start. The response of the carcinoma was quite different. After two applications it was smaller and the tissue had become soft and necrotic. After the fourth treatment small, discrete, bilateral epitrochlear nodes were detected. It was believed that these were inflammatory, and the course of therapy was con-

Fig. 5 (case 2).—Appearance of the lesions shown in figure 4 on March 1, one week after the course of podophyllin had been completed. The keratoses are unchanged, but the carcinoma has lost its keratotic surface and has flattened while extending peripherally.

tinued. With successive applications the lesion flattened, at the same time extending peripherally. After the fourteenth application a piece of tissue was excised and histologic examination showed residual tumor. Superficial hyaline necrosis with underlying hydropic degeneration of the prickle cells was present. Some of the basal cells showed a breakdown of their nuclei with an irregular condensation of the chromatin in a manner resembling that seen in the "podophyllin cell" described by Sullivan and King. Treatment was completed on February 22, at which time the tumor measured 2.5 by 2.5 cm., was flat topped and slightly elevated, with a soft, red, granulomatous surface (fig. 5). On February 24 it was noted that the left epitrochlear glands had increased in size and that a moderately large gland was present in the left axilla. Because of the possibility of metastases the patient was hospitalized and on March 6 excision of the tumor plus radical dissection of the

lymph channels of the left arm and axilla was performed. Microscopic examination of the lymphatic tissue showed only chronic inflammation. Sections of the treated area revealed a well differentiated tumor manifested by irregular columns and masses of cells showing only slight anaplasia and even retaining intercellular bridges. The degenerative changes seen in the preceding biopsy were not apparent.

COMMENT

Although treatment in both cases was considered a failure in that there was not complete eradication of the tumor, the cancerocidal action of podophyllin was demonstrated in each. In the first case, a large basal cell epithelioma was destroyed except for one small area. In the second, striking changes were noted grossly and microscopically after the applications of podophyllin; observation of degenerative cytologic changes similar to those reported by Sullivan and King and the trend toward greater differentiation of the tumor cells indicated that the drug did in some way interfere with the normal progression of the carcinoma.

Stimulated by the encouraging results reported in the treatment of experimental and human malignant growths with podophyllin, we originally intended to use the drug in treatment of a large series of cutaneous carcinomas. However, our observations in these first two cases led us to conclude that although podophyllin does have a destructive action on the cells of cutaneous carcinoma, the extent and degree of such action could not be regulated so as to insure total destruction of all tumor cells. This conclusion was supported by Sullivan's recent report [12] that 15 of the tumors he had treated with podophyllin [11] had recurred. Therefore, plans for continuing the investigation of the use of podophyllin in the treatment of cutaneous carcinoma have been discarded.

SUMMARY

1. Studies concerning the effect of podophyllin (resin of podophyllum N.F.) on normal and abnormal cells are reviewed.

2. Two cases of cutaneous carcinoma unsuccessfully treated by topical application of podophyllin are reported.

3. Chemotherapy with podophyllin is believed to be an unreliable procedure for the treatment of cutaneous carcinoma.

Photographs were taken by Mr. George Mancini.

247 Waterman Street (Dr. Kern).

Rhode Island Hospital (Dr. Fanger).

12. Sullivan, M., in discussion on Zell, L. M., and Sullivan, M.: Multiple Benign Cystic Epithelioma, Atlantic Dermatologic Conference, Baltimore, Md., March 25, 1950.

EFFECTIVENESS OF ANTICHANCROIDAL DRUGS TESTED BY HETEROINOCULATION OF BUBO FLUID FROM UNTREATED DONOR

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THE EFFECTIVENESS of antichancroidal drugs in experimental chancroid of man has been tested by three methods: (*a*) by autoinoculation, i. e. by intradermal injection into the forearm of fluid taken from a chancroidal bubo of the same patient, after which the patient is treated with appropriate drugs, and observation of whether the experimental infection does or does not develop; (*b*) by injection of such fluid from an untreated person into volunteers and treatment of the recipients with the different drugs to be tested, and (*c*) by treatment of the donor and, afterward, inoculation of others with bubo fluid from the treated person.

With method *a*, if significant figures are to obtained, a substantial number of persons with chancroidal buboes is required and, unless method *b* is used also, there are no proper controls. Method *c* can be controlled, again by employing method *b* on a small series at the outset, and is a satisfactory method inasmuch as only 1 donor is required for each drug to be tested. Method *b* gives even better scientific results for, if necessary, a very large number of controls and recipients treated with various drugs may be inoculated with bubo fluid simultaneously. Very rapid results, therefore, may be obtained with its use.

The results of work undertaken during 1949 employing methods *a* and *c* have already been described.[1] The present paper concerns method *b*.

TECHNIC

An injection of 0.05 ml. of bubo fluid is administered intradermally into the forearms of volunteers. A small number of recipients are left untreated to act as controls. In these cases a small tender papule, or a diffuse tender erythema, will develop in twenty-four hours, becoming a definite tender papule at forty-eight to seventy-two hours and then proceeding to pustulation, after which it may be needled. The presence of pus indicates a "take." If the patient is then treated

1. Willcox, R. R.: Effectiveness of Anti-Chancroidal Drugs Tested by Auto-Inoculation of Bubo Fluid, Am. J. Syph., to be published; Effectiveness of Anti-chancroidal Drugs Tested by Heteroinoculation from the Treated Donor, Brit. J. Ven. Dis., to be published.

with effective drugs the process progresses no further provided the inoculum has been kept small as suggested. If untreated it proceeds to the formation of a definite ulcer which may be cured by appropriate drugs, but this development is to be avoided.

In the treated subject, however, no such reaction occurs apart from the occasional presence of a nontender papule at forty-eight hours. If the treatment has been inadequate this papule may persist and ulcerate later. On this account, therefore, in all persons showing persistent papules the lesions should be needled for the presence of pus, and, even if it is not observed, such persons should be given treatment with effective drugs when surveillance is deemed complete.

The experiments were performed with material taken from 10 patients with chancroidal buboes. Bubo fluid from these donors was injected into 90 persons who were then treated with various drugs and into 30 untreated controls. The controls included 6 persons who were inoculated with material from their own buboes and acted as common controls for methods *a* and *b*. The recipients were treated with various drugs as follows: sulfonamides, 15; streptomycin, 7; aureomycin, 10; chloramphenicol, 4; anthiomaline® (lithium antimony [trivalent] thiomalate prepared as a 6 per cent solution, 1 cc. of which contains about 0.01 Gm. of antimony), 3; neoarsphenamine, 11; penicillin in oil and wax, 20; "single shot" treatment with procaine penicillin with 2 per cent aluminum monostearate, 16, and orally administered penicillin, 4.

TABLE 1.—*Results of Dmelcos Skin Tests (Intradermal Tests with a Vaccine of Hemophilus Ducreyi)*

Result	"Takes"	Non-"Takes"
Positive	12	16
Doubtful	2	4
Negative	27	43
No record	4	12
Per cent positive	29.3	25.4

SUBJECTS

Donors.—All 10 donors were African Negroes with chancroidal sores proved negative for syphilis by repeated dark field examinations. The Wassermann reactions were positive in 1, negative in 6 and not recorded in 3. The Dmelcos skin test (for chancroid) gave positive results in 5, doubtful in 1 and negative in 3. For 1 the result was not recorded.

Recipients.—All 120 recipients were Negroes with venereal disease, usually syphilis and often soft sore alone or in combination, which disease was extremely prevalent in the area where these experiments were conducted. The results of the Wassermann tests are available for 100 of the 120 recipients and were positive for 30 and negative for 70. The results of the Dmelcos skin tests for both "takes" and non-"takes" are appended (table 1).

Thus, in this series there was no evidence that the presence of positivity in the Dmelcos test offered any degree of immunity toward the experimental chancroidal infection.

EXPERIMENTS

EXPERIMENT 1.—Experiment 1 consisted in injections of bubo fluid from a Dmelcos-negative donor into 2 untreated controls in addition to himself and 19 others treated by various means. Four were given sulfathiazole, 4 Gm. daily, having already been under treatment for none to three days at the time of inoculation; 2 were treated with 0.5 Gm. of streptomycin daily for four and five days, respectively; 4 had aureomycin, 1 receiving three 250 mg. capsules orally on the first day followed by two on the second day, 2 being given one 250 mg. capsule daily for two days and 1 receiving the same dose daily for four days, having had two days of treatment prior to inoculation. Nine others were under treatment for syphilis with eight daily injections of 600,000 units of penicillin in oil and wax, having received from none to four doses at the time of inoculation.

Results.—The 3 untreated controls all had "takes," but no reaction was noted in all 4 treated with sulfathiazole, in both receiving streptomycin or in all 4 given aureomycin. None of those treated with eight daily injections of penicillin in oil and wax were likewise regarded as having definite "takes" although 1 person showing a well marked nontender bump at 120 hours was considered not to have a "take" and another with a slightly tender bump at 120 hours, which was needled but found not to contain pus, must be regarded as showing doubtful reactions.

EXPERIMENT 2.—Material from a donor (no record of the Dmelcos test) was inoculated into 4 untreated persons in addition to the donor, all of whom were left untreated, and into 26 others treated by various means. Eight were given sulfathiazole, 4 Gm. daily, having commenced treatment none to seven days previously; 2 received 250 mg. of aureomycin orally twice daily for two days; 1 had a single injection of 0.45 Gm. of neoarsphenamine; another, 0.45 Gm. of neoarsphenamine immediately, followed by 0.15 Gm. daily for two days; another received 1 Gm. of streptomycin daily for six days, being inoculated on the second day, while yet another had 0.5 Gm. of streptomycin twice daily for one day followed by the same dose given once on the following day. Eleven were under treatment for syphilis with eight daily injections of penicillin in oil and wax, having, at the time of inoculation, received one to two doses (9 subjects) and three to five doses (2 persons). One received daily doses of 2 cc. of anthiomaline,® being inoculated at the time of the third dose.

Results.—There were "takes" for 4 of the 5 controls, including the donor. The 1 patient treated with anthiomaline® also showed a "take," as did 1 of 2 treated with neoarsphenamine (the one receiving three injections for a total of 0.75 Gm. in three days). The 8 persons treated with sulfathiazole, the 2 with streptomycin, the 2 with aureomycin and the 11 with penicillin in oil and wax all failed to show a "take" although 1 of the penicillin-treated subjects and 1 of the streptomycin-treated persons showed a nontender bump at 96 hours.

EXPERIMENT 3.—Material from a Dmelcos-doubtful donor, who had already received two injections of 0.45 Gm. of neoarsphenamine, was injected into himself as a control and into 7 other persons. Two of the latter were given sulfonamides (sulfathiazole, 4 Gm. daily for one week, commenced simultaneously); 3 received weekly injections of 0.45 to 0.6 Gm. of neoarsphenamine and 0.2 Gm. of bismuth, having received from one to six injections of both drugs at the time of inoculation, and two were treated with antimony preparations. One of these commenced treatment with injections of 1 grain (60 mg.) of sodium antimonyl tartrate on alternate days simultaneously with inoculation, and the other, having had three such doses in the five days prior to inoculation, continued such treatment on alternate days for the duration of the test.

Results.—The control, 2 of the 3 neoarsphenamine-treated subjects and both of the antimony-treated persons had a "take." One of the sulfathiazole-treated subjects manifested a large papule still present at 120 to 144 hours but which aborted without visible formation of pus although at one time it appeared as if suppuration was about to take place. The other showed an extremely angry tender erythema at 24 hours which persisted for two days and necessitated the keeping of the arm in a sling. The condition, however, subsided as treatment with the sulfonamides was continued, and the reactions in both of these cases were classified as doubtful.

EXPERIMENT 4.—Pus from a Dmelcos-positive donor was injected into himself and into 2 other untreated persons. It was also injected into 5 other volunteers, of whom 3 received 0.45 Gm. of neoarsphenamine at the time of inoculation and again two days later; 1 was on the sixth day of a week's course of 4 Gm. of sulfathiazole daily, which course was continued for another day, and 1 had a simultaneous injection of 2,400,000 units of procaine penicillin G with 2 per cent aluminium monostearate.

Results.—The 3 controls all showed a "take," as did 1 of the 3 neoarsphenamine-treated subjects, in whom the "take" was delayed until the fifth day. Two treated with neoarsphenamine, 1 with sulfathiazole and 1 with procaine penicillin with aluminium monostearate showed no "take."

EXPERIMENT 5.—Pus from a Dmelcos-positive donor was inoculated into himself, into 5 untreated controls and also into 12 recipients treated in 2 instances with 250 mg. of aureomycin orally twice daily for two days, in 2 with 1 Gm. of streptomycin twice daily for one day followed by administration of 0.5 Gm. twice daily for two days, in 1 with 0.45 Gm. of neoarsphenamine given simultaneously with inoculation and the same dose three days later, and in 7 treated with single injections of 2,400,000 units of procaine penicillin G with 2 per cent aluminium monostearate given one, four, four, five, seven, seven and eight days, respectively, prior to inoculation.

Results.—Five of the 6 controls showed a "take," as did the 1 person given neoarsphenamine and 5 of the 7 given the penicillin four, four, five, seven and eight days previously.

EXPERIMENT 6.—Bubo pus was injected into the donor (himself Dmelcos-negative), 2 other controls and 8 persons treated with single injections of 2,400,000 units of procaine penicillin G with 2 per cent aluminium monostearate given one, two, three, four, six, seven, seven and eight days prior to inoculation.

Results.—The 3 controls all showed a "take," as did 3 of those given the penicillin seven, seven and eight days previously.

EXPERIMENT 7.—Pus from a Dmelcos-positive donor was injected into 1 volunteer control and into 1 person who was given 0.25 Gm. of chloramphenicol (chloromycetin®) orally three times daily for two days followed by the same dose twice daily for two days.

Results.—The control showed a mild "take" at 48 hours, but nothing abnormal was noted in the chloramphenicol-treated subject.

EXPERIMENT 8.—Pus from another Dmelcos-positive donor was injected into 4 persons, 2 of whom were left untreated. One was given 0.25 Gm. of chloramphenicol three times a day for one day followed by 0.25 Gm. twice daily for two days, and the other received 200,000 units of calcium penicillin in a buffered tablet orally three times a day for four days.

Results.—One of the 2 controls and the person given oral penicillin had a "take."

EXPERIMENT 9.—Material from yet another Dmelcos-positive donor was injected into 3 untreated persons and also into 3 others given 100,000 units of calcium penicillin in a buffered tablet orally four times a day (400,000 units daily) for three days.

Results.—The three untreated controls showed "takes," while the 3 persons receiving orally administered penicillin did not.

EXPERIMENT 10.—Pus from another Dmelcos-negative donor was inoculated into 3 untreated controls and into 2 persons given 250 mg. of aureomycin orally twice daily for two days, into 2 others given chloramphenicol, 0.25 Gm., three times daily for four days, into 1 who received 0.5 Gm. of streptomycin twice daily for three days and into 2 who were treated with neoarsphenamine. Of the last-mentioned subjects, 1 had a single injection of 0.45 Gm. and the other the same dose at the time of inoculation followed by 0.3 Gm. given three days later.

Results.—The 3 untreated controls all had "takes," as did the neoarsphenamine-treated person receiving two injections. One neoarsphenamine-treated person, 1 receiving streptomycin, the 2 receiving aureomycin and the 2 receiving chloromycetin did not have "takes."

DRUGS

The results of the foregoing experiments have been regrouped according to the drugs administered, as follows:

Sulfonamides (15 cases: experiments 1, 2, 3 and 4).—In the 12 untreated controls in this series of experiments there were 11 "takes." When fluid from these 4 donors was injected into 15 persons treated with 4 Gm. of sulfathiazole daily for one week, on any day of the course from 1 to 7 there were no definite "takes." Two doubtful reactions, with angry lesions presented within twenty-four to forty-eight hours but which subsided without pustulation, were noted in 2 persons who commenced treatment simultaneously with inoculation. Sulfathiazole thus proved an effective prophylactic against the experimental infection.

Streptomycin (7 cases: experiments 1, 2, 5 and 10).—In the 17 controls in this series there were 15 "takes." Seven inoculated persons were treated with streptomycin in total doses of 1.5 to 6.0 Gm. given over two to five days. None of these had a "take" although 1 showed a persistent nontender bump at 96 hours. Streptomycin thus also proved an effective prophylactic.

Aureomycin (10 cases: experiments 1, 2, 5 and 10).—In the 17 controls in this series of experiments there were 15 "takes." The doses of aureomycin given to 10 persons varied from 500 mg. to 1,250 mg. given orally over two to four days (in 6 the dose was 250 mg. twice daily for two days). None of these persons had a "take," and aureomycin was thus also effective in preventing an experimental infection.

Chloramphenicol (4 cases: experiments 7, 8 and 10).—In the 6 controls in this series there were 5 "takes." Four inoculated persons received from seven to twelve capsules each of 0.25 Gm. of chloromycetin orally over three to five days. Not 1 had a "take," and thus chloramphenicol also proved an efficient prophylactic.

Antimony Preparations (3 cases: experiments 2 and 3).—Five out of 6 controls in this series showed a "take." Material from 1 donor was inoculated into 1 person receiving daily injections of anthiomaline® at the time of the third dose and into 2 persons receiving 1 grain of sodium antimonyl tartrate on alternate days—with a "take" in all 3. Antimony preparations are not considered effective prophylactics.

Neoarsphenamine (11 cases: experiments 2, 3, 4, 5 and 10).—There were 16 "takes" in the 18 controls of this series. Inoculations were made into 11 persons treated with neoarsphenamine. Three of these had received one to six doses of 0.45 to 0.6 Gm. with 0.2 Gm. of a bismuth preparation before inoculation, and in 8 the treatment commenced simultaneously with inoculation and consisted in 0.45 to 0.9 Gm. of neoarsphenamine given over twenty-four to seventy-two hours. No less than 6 subjects showed a "take," and, in general, the "takes" occurred in the persons who had been given the larger amounts. Two of the 3 who received a bismuth preparation in addition showed a "take." Both neoarsphenamine and bismuth preparations, therefore, are considered inefficient prophylactics.

Penicillin.—Three types of penicillin administration were tested. These were (1) eight daily injections of 600,000 units of penicillin in oil and wax, (2) single injections of 2,400,000 units of procaine penicillin G with 2 per cent aluminium monostearate and (3) orally administered penicillin in doses of 400,000 to 600,000 units given over three to four days.

Penicillin in Oil and Wax (20 cases: experiments 1 and 2): In 8 untreated controls there were 7 "takes." Of 20 persons inoculated while under treatment with eight daily injections of 600,000 units of penicillin in oil and wax 14 had received from none to two doses at the time of inoculation and 6, three to five doses. Although 2, in whom treatment had been commenced at the time of the third and fourth dose, respectively, had persistent nontender papules, there were definite "takes" in none.

Procaine Penicillin G with Aluminium Monostearate, "Single Shot" (16 cases: experiments 4, 5 and 6): In 12 controls in this series there were 11 takes. This method of penicillin administration proved effective in preventing experimental soft sore in 6 out of 8 persons inoculated with chancroidal material one to four days after receiving a "single shot" of 2,400,000 units of procaine penicillin G with 2 per cent aluminium monostearate but in only 2 of 8 inoculated five to eight days afterward. Serum estimations performed on other African patients in this clinic showed that detectable penicillin levels could be obtained for nine days after such a single injection of the preparation that was used. It is evident, therefore, that in those persons who had a "take" penicillin was present in the serum but that the level was too low and

insufficiently sustained to prevent experimental chancroid. On the other hand, the level produced by daily injections of 600,000 units of penicillin in oil and wax was capable of preventing the disease.

Orally Administered Penicillin (4 cases: experiments 8 and 9): Four out of 5 untreated controls showed a "take," and 1 other "take" was produced in 1 of 4 persons given 400,000 to 600,000 units of calcium penicillin in buffered tablets orally over 3 to 4 days. These data appear to confirm the contention that penicillin has some prophylactic value against chancroid but that the serum level has to be high and sustained for the drug to be completely successful.

TABLE 2.—*Summary of Results of the Ten Experiments*

Drug	No. of Experiments	Total No. Inoculated	"Takes"	No "Takes"
Controls	10	30	27	3
Sulfathiazole	4	15	0	15 (2 doubtful)
Streptomycin	4	7	0	7 (1 doubtful)
Aureomycin	4	10	0	10
Chloramphenicol	3	4	0	4
Antimony	2	3	3	0
Neoarsphenamine	5	11	6	5
Penicillin in oil and wax	2	20	0	20 (2 doubtful)
Penicillin with aluminum monostearate	4	16	8	8
Penicillin given orally	2	4	1	3

SUMMARY AND CONCLUSIONS

The technic of testing antichancroidal drugs by assessing their power of preventing experimental infection in human volunteers inoculated with bubo fluid of tested virulence has been described.

In ten experiments 90 persons were inoculated and then treated with one of nine treatment schedules. Thirty untreated persons acted as controls.

Sulfathiazole, streptomycin, aureomycin and chloramphenicol proved efficient systemic prophylactics against the experimental chancroidal infection. Antimonials, bismuth preparations and neoarsphenamine proved ineffectual. Penicillin, if given in such a manner as to produce and maintain a high serum concentration, was also effective but not so when given by other means, when it was successful only in a portion of the cases.

The utilization of such a technic can give clearcut results in a minimum of time, and only a few cases of chancroidal bubo are necessary for its performance.

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Material used in the tests was provided by Burroughs Wellcome & Co., London, and Boots Pure Drug Co., Ltd., Nottingham, England.

DISCUSSION OF TATTOO REACTIONS WITH REPORT OF A CASE SHOWING A REACTION TO A GREEN COLOR

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REACTIONS developing at the site of tattoos can be conveniently subdivided into those which arise because of accidents incident to the tattooing process and those which develop because of the deposition of foreign material. Under the first category come the various infections which have been transmitted by this procedure. Under the second category (disregarding the immediate inflammatory reaction which is commonly seen in all tattoos) there are three types of reactions: (1) the development of a locus minoris resistentiae or the alteration of the area in some way so as to predispose it to the localization of various skin diseases, e. g., psoriasis, lupus erythematosus and lichen planus; (2) the development of a foreign body type of reaction presumably arising as a response to the alien material, and (3) the development of an allergic sensitization to one of the introduced colors.

REVIEW OF THE LITERATURE

Unna,[1] Ballin,[2] Sulzberger,[3] Müller,[4] Madden,[5] Novy,[6] Sulzberger, Kanof and Baer [7] and Swinny [8] all reported cases of the allergic type of

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1. Unna, P., Jr.: Quecksilberüberempfindlichkeit und Tätowierung, Arch. f. Dermat. u. Syph. **160**:153, 1930.

2. Ballin, D. B.: Cutaneous Hypersensitivity to Mercury from Tattooing: Report of Case, Arch. Dermat. & Syph. **27**:292 (Feb.) 1933.

3. Sulzberger, M. B.: Tattoo Dermatitis (Sensitivity to Cinnabar?), Arch. Dermat. & Syph. **36**:1265 (Dec.) 1937.

4. Müller, O.: Über einen Fall von Hautgeschwulstbildungen auf dem Boden einer Tätowierung, Dermat. Wchnschr. **106**:6 (Jan. 1) 1938.

5. Madden, J. F.: Reactions in Tattoos, Arch. Dermat. & Syph. **40**:256 (Aug.) 1939.

reaction. The reported reactions appear to have arisen because of the development of an allergic sensitization to the cinnabar used to produce the red color of the design. In several of the patients positive reactions to patch tests with mercury in one or another form were obtained.

Fig. 1.—Photograph of tattoo, showing inflamed areas. The design contained three colors—red, blue and green—but the inflammation was limited to the green areas.

REPORT OF CASE

A 34 year old white man was admitted to Percy Jones General Hospital, Battle Creek, Mich., because of a more or less generalized dermatitis. This was diagnosed as neurodermatitis disseminata (atopic dermatitis). In the course of examination of

6. Novy, F. G., Jr.: Generalized Mercurial (Cinnabar) Reaction Following Tattooing, Arch. Dermat. & Syph. **49**:172 (March) 1944.

7. Sulzberger, M. B.; Kanof, A., and Baer, R. L.: Complications Following Tattooing: Sensitization and Desensitization to Mercury; Report of Case, U. S. Nav. M. Bull. **43**:889 (Nov.) 1944.

8. Swinny, B.: Generalized Chronic Dermatitis Due to Tattoo; Report of Case, Ann. Allergy **4**:295 (July-Aug.) 1946.

his skin, it was noticed that he had a tattoo on his upper left arm in which certain areas were inflamed and swollen. As can be seen from the accompanying photograph (fig. 1), the design was that of an eagle and consisted of three different colors, red, blue and green. The inflamed areas, however, were limited to the green portions. As far as the patient recollected, the tattoo had been done about eight years previously and had not bothered him until about six months ago, at which time the green areas began to swell; occasionally there was a superficial ulceration which would yield a small slough. After a portion of the tattoo had been removed for pathologic study, the remaining green portions were excised. After the removal the patient had no further trouble with the tattoo.

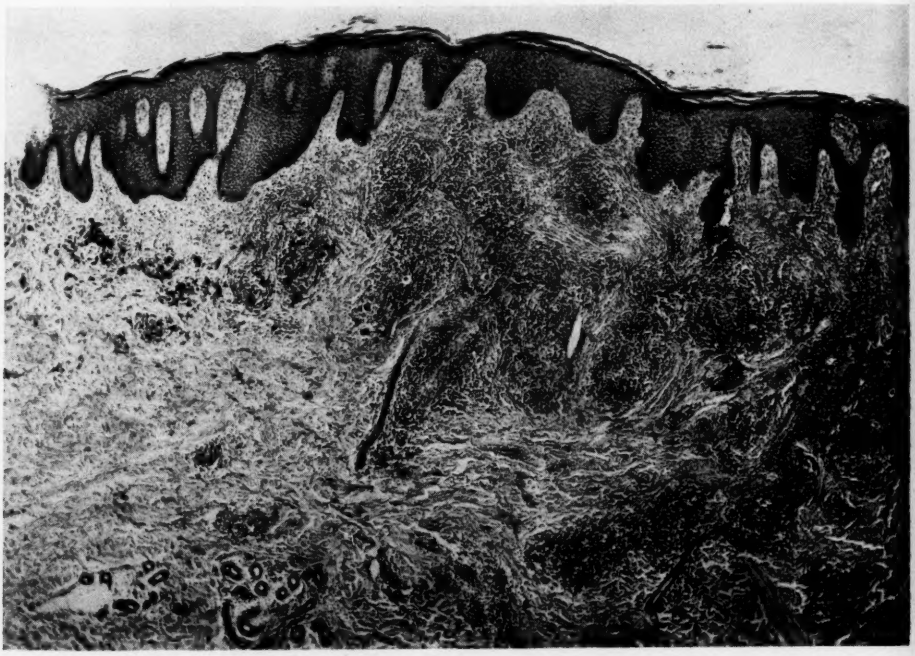

Fig. 2.—Horizontal wide band composed of circumscribed nests of cellular infiltrate; hematoxylin and eosin stain, × 36.

HISTOPATHOLOGIC REPORT

The epidermis showed irregular acanthosis and edema. There was a thin scale in which there were small islands of parakeratosis directly over areas of interruption of the granular layer. The suprapapillary rete was thickened; the rete pegs were irregularly elongated, thickened and fused, and the basal layer was intact. Throughout the epidermis there was a moderate degree of spongiosis, and there was a spotty intracellular edema which in places showed coalescence to form microscopic intraepi-

dermal vesicles. In the papillae the blood vessels were dilated, and there was a diffuse, slight infiltrate of lymphocytes, histiocytes and connective tissue cells which in places had invaded the epidermis. These are the histologic features of chronic neurodermatitis, which the patient had, and they had nothing to do with the tattoo reaction.

In the midcorium, extending from the subpapillary layer to the level of the sweat glands, there was a wide horizontal band composed of circumscribed masses of cellular infiltrate (fig. 2). Each of these

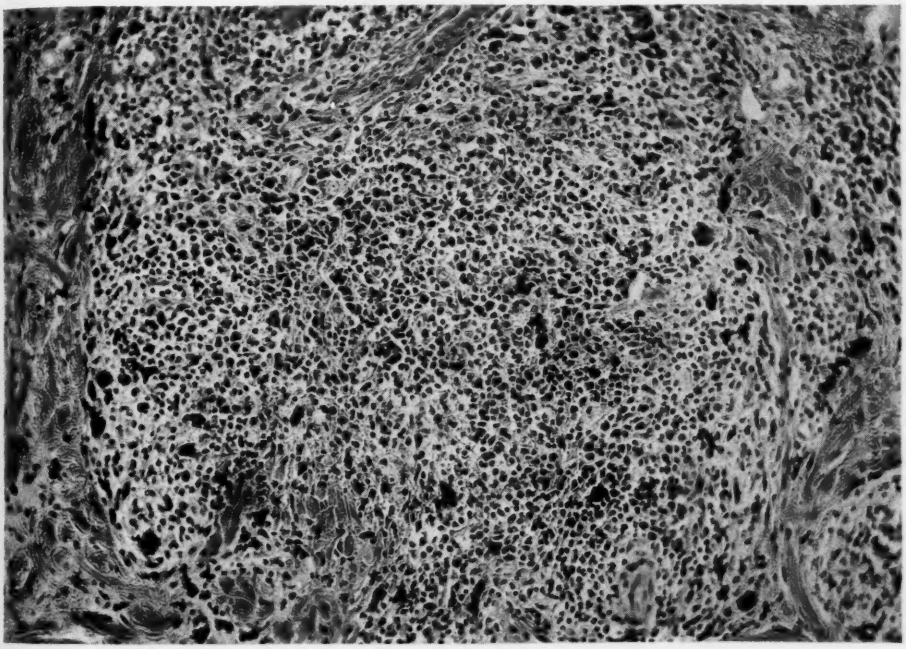

Fig. 3.—Cellular infiltrate about the pigment granules, containing lymphocytes, plasma cells and many eosinophilic cells; hematoxylin and eosin stain, × 161.

enclosed considerable dark pigment of a greenish hue. The pigment occurred in the form of large clumps and also as diffuse minute free granules, but much of it was massed within large chromatophores. Some of these pigment-laden cells were elongated, but many were very large and irregularly rounded. Aside from the chromatophores, the infiltrate (fig. 3) was composed largely of lymphocytes with an admixture of a few plasma cells and very many eosinophilic cells, the latter being more evident in the section stained with Giemsa stain. These cellular masses were sharply circumscribed and were separated by connective

tissue that showed very little evidence of inflammation even though it contained much pigment both within cells and as free granules. At one end of the section there was also considerable pigment present along the wall of a blood vessel, within chromatophores and lying free in the tissues, but in this area there was no evidence of an inflammatory reaction (fig. 4). Staining with Perle's reaction showed no hematogenous pigment. Examination of the section under a polarizing microscope failed to demonstrate any doubly refractile particles.

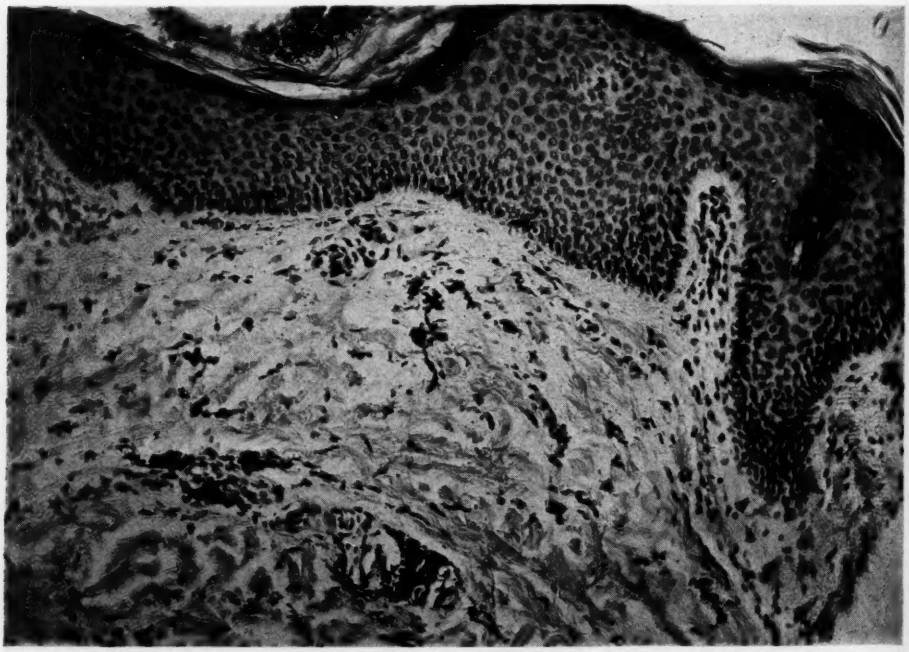

Fig. 4.—Pigment granules about the blood vessels and lying free in the tissues without any accompanying inflammatory reaction; hematoxylin and eosin stain, × 161.

The hair follicles, sebaceous glands, smooth muscles, sweat glands, deeper part of the corium and hypoderm showed no pathologic changes.

The inflammatory reaction present was not of the type ordinarily provoked by silica or other mineral particles, for the epithelioid cells and giant cells generally seen in the foreign body sarcoid type of reactions were absent. The failure to find doubly refractile particles with the polarizing microscope would indicate that silica was not present. The profusion of eosinophilic cells in the infiltrate suggested an allergic response.

It is difficult to reconcile the inflammatory reaction to the pigment seen in much of the specimen with the lack of response at one end of the specimen and also with the lack of response in the intervening connective tissue to pigment granules that seemed to be identical with those that apparently provoked the reaction. While in the sections examined the pigment in all parts had a greenish hue and appeared to be the same, it is, of course, possible that the various pigment particles may actually have been of more than one chemical nature. Unfortunately, histochemical or other means of identifying the pigment granules in the tissues could not be used.

MATERIALS USED TO PRODUCE TATTOO DESIGNS

In view of the fact that our patient was apparently the first reported who reacted to a greenish pigment, we endeavored to determine the nature of this pigment. The patient recalled where the tattoo had been done, but the tattooer could not be located. For a variety of reasons, it was not possible to examine the excised material directly and determine the nature of the pigment. We accordingly made a search of the literature for information regarding the pigments that are used in tattoos and found this to be very sparse. Through the courtesy of the Food and Drug Administration, Federal Security Agency, Washington, D. C., and of Fezandie and Sperrle, Inc., of New York, N. Y., we obtained the names and, in part, the chemical composition of the materials used for tattoo designs. In view of the fact that these are not generally known, we think it worth while to list the various substances with some information about them.

In the appendix are enumerated the substances used to produce the different colors in tattooing as done by lay artists.[9] It should be realized that these substances are sold under a great variety of trade names and code numbers. However, regardless of the name used, the materials listed are, so far as we could determine, the ones employed to obtain the named different colors and shades seen in tattoo designs. Another point to be borne in mind is that the pigments employed can be obtained in varying degrees of purity and, consequently, the color range for any given compound can vary considerably. The nature and dilution of the fluid used to make the paste that is actually put on the tattoo needle also influence the shade obtained.

SUMMARY AND CONCLUSIONS

A case is reported of a cutaneous reaction developing at the areas of green color in a tattoo design. The reaction developed about eight years after the tattoo was done.

9. For medical tattooing, other substances may be employed, e. g., gold and platinum salts.

The histopathologic features present would seem to indicate that the reaction probably arose because of the development of an allergic sensitization to the green material.

APPENDIX

PIGMENTS OR DYES USED TO PRODUCE DIFFERENT COLORS IN TATTOOS

BLACKS

Carbon.—Finely dispersed carbon in an ammoniacal solution. Phenol is also usually present.

Iron Oxide (C. I. 1311).* Also known as black oxide and magnetic oxide. It is ferroso-ferric oxide (Fe_3O_4 or $FeO \cdot Fe_2O_3$ or $Fe(OH)_2 \cdot Fe_2O_3$).

Logwood.—Probably logwood black (C. I. 1253), also known as campeachy black, diamond black and neutral black and by many other names. This is an extract of logwood from the tree Haematoxylon campechianum. It is made into a lake with potassium dichromate, so that as it is applied there is a considerable amount of chromate present.

BLUE

Cobaltous Aluminate (C. I. 1285).—$CoO\ Al_2O_3$, also known as azure blue and cobalt ultramarine and by many other names.

BROWN

Ochre (C.I. 1267).—A natural ferric hydrate and basic ferric sulfate containing alumina, silica and lime, among other substances. It occurs in a wide variety of shades and is sold under many names, including ochre, with all sorts of descriptive adjectives, such as flame ochre and imperial ochre. It is also known as Chinese yellow, imperial yellow, sienna, mahogany brown, Roman earth, Mars yellow, Mars orange, Mars red, Mars brown.

FLESH

Iron Oxides.—These, as a rule, are impure and are a variety of ochre (see under Brown).

GREEN

Chrome Oxide Green (C.I. 1291).—Chromic oxide or chromium sesquioxide (Cr_2O_3), also known as casalis green.

Guignet's Green (C.I. 1292).—Hydrated chromium sesquioxide $Cr_2O(OH)_4$ or mixtures of $Cr_4O_5(OH)_6$ and $Cr_4O(OH)_{10}$ with Cr_2O_3 together with 0.5 to 10 per cent of boric acid. It is also known as emerald green and pannetiers green.

Phthalocyanine Dyes.—Usually as copper salts and sometimes mixed with other coal tar dyes, especially Hansa yellow G (fanchon yellow; ext. D & C yellow #5 †), which is alpha-(O-Nitro-p-tolylazo)-acetoacetanilide.

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*The expression, C. I. 1311, stands for "Colour Index" no. 1311, and similarly for the other C. I. numbers. The "Colour Index" is the outstanding source of information in English on dyes and pigments. It is edited by F. M. Rowe and published by the Society of Dyers and Colourists, Yorkshire, England.

† Ext. D & C yellow #5 refers to the official designation as it appears in the Coal Tar Color Regulations issued by the Food and Drug Administration, Federal Security Agency.

RED

Cadmium Selenide.—Also known as cadmium red (see C.I. 1272).
Cinnabar (C.I. 1280).—Mercuric sulfide (HgS).
Sienna (C.I. 1267).—See ochre under Brown.

VIOLET

Manganese Violet.—(Probably) $NH_4Mn_2(P_2O_7)_2$.

WHITE

Titanium White (C.I. 1264).—Titanium dioxide (TiO_2).
Zinc White (C.I. 1262).—Zinc Oxide (ZnO), also known as Chinese white.

YELLOW

Cadmium Yellow (C.I. 1272).—Cadmium sulfide (CdS), also known as radiant yellow. It may be also mixed with zinc sulfide and barium sulfate.
Ochre (C.I. 1267).—See under Brown.

HISTOPATHOLOGIC RESPONSE OF THE SKIN TO GELFOAM®

DAVID R. TAYLOR, M.D.
AND
LEO KAPLAN, M.D.
LOS ANGELES

OBTAINING hemostasis is a basic surgical technic and has been achieved by many mechanical means. The more recent advances in the management of capillary and venous oozing have been the utilization of coagulating agents such as thrombin with an absorbable substance which will serve as a matrix for the formation of a clot.

During the recent world war the department of physical chemistry of the Harvard Medical School, through its large scale plasma fractionation program, produced a very significant contribution to hemostasis in the form of fibrin foam. Fibrin foam was utilized in experimental and neurosurgical procedures with gratifying results. It was found that fibrin foam soaked in thrombin possessed a hemostatic effect and produced a minimal amount of tissue reaction.

Foreseeing the possibility of the nationwide program of human blood donations coming to an end at the cessation of hostilities, with a consequent reduction in the supply of fibrin, two chemists, Correll and Wise,[1] began in 1944 to search for a substitute material to replace fibrin. They found a worthy replacement in gelatin. Gelatin has been referred to as a "universal protein" because it can be procured from any animal and is devoid of antigenicity. It is obtained by boiling collagen in water or acid.

Gelatin is an unusual protein, rich in aminoacetic acid (glycocol), proline (alpha-pyrrolidin carboxylic acid) and arginine (aminoguanidine valerianic acid), but low or entirely lacking in the amino acids containing aromatic radicals on which the anaphylactic and precipitin reactions depend. Gelatin is nontoxic and has lost all trace of

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Correll, J. T., and Wise, E. C.: Certain Properties of a New Physiologically Absorbable Sponge, Proc. Soc. Exper. Biol. & Med. **58**:233-235 (March) 1945.

its species identification. It is not satisfactory as the sole dietary protein, as it is deficient in certain essential amino acids.

Beef is the usual source of the commercial gelatin from which Correll and Wise developed their absorbable spongelike matrix which they called gelfoam.® This matrix is utilized as a thrombin carrier for purposes of hemostasis. The commercial gelatin is converted from a soluble substance into an insoluble but absorbable material. It is made up in a solution to which a hardening agent is added. Bubbles of air are introduced, and the mixture is allowed to air dry in monel® metal forms and then sterilized before biologic use.

The resultant product is light, off white, nonelastic, tough and very porous and can be molded or cut into any desired shape or form. A section can be moistened and will take up 50 times its weight in water when submerged and the air bubbles expressed. The substance does not fragment readily.

Ordinarily five to eight minutes is the normal range of time for a normal blood clot to form. If the clot attaches itself with sufficient firmness and if the after-coming pressure is not too great, the flow of blood is effectively checked. A small increase in the magnitude of the hemorrhage alters the situation.

Gelfoam® almost instantly controls capillary oozing or bleeding from veins and provides a saving of time to the busy surgeon as well as a means of good hemostasis.

The sponge can be used with or without thrombin. Jenkins and associates [2] postulated that the sponge per se was responsible for a substantial part of the hemostatic actions. They stated that it is possible that the enormous surface area of the myriads of interstices may attract and damage the platelets in the blood which enters the sponge, thus liberating thromboplastin. This, in combination with the calcium and prothrombin in the blood, may elaborate enough thrombin to initiate the clotting mechanism. The addition of prepared thrombin, according to these authors, undoubtedly enhances and accelerates the hemostatic action of gelatin sponge, but they stated that they were not prepared to estimate the extent to which it does.

Animal experiments demonstrated that the sponge is absorbed in four to six weeks when implanted in various tissues. Thrombin and damp gelatin implants into rat muscle found the gelfoam® to be absorbed by the thirtieth postoperative day. The histologic reaction was recorded by Correll and associates [3] to have been no greater a cellular infiltration

2. Jenkins, H. P.; Janda, R., and Clarke, J. S.: Clinical and Experimental Observations on Use of Gelatin Sponge or Foam, Surgery **20**:124-132 (July) 1946.

3. Correll, J. T.; Prentice, H. R., and Wise, E. C.: Biologic Investigation of a New Absorbable Sponge, Surg., Gynec. & Obst. **81**:585-589 (Nov.) 1945.

than occurs with the resorption of an ordinary blood clot. Pilcher and co-workers [4] recorded similar results.

Histopathologic studies by Jenkins and Clarke [5] of gelfoam® implants into the liver, kidneys and spleen revealed the gelatin sponge appearing as a meshwork of homogenous hematoxylin-staining material. These authors noted that when polymorphonuclear cells were present there was evidence of absorption of the sponge. Most sections demonstrated polymorphonuclear cells. In addition, there were also some lymphocytes and plasma cells. After a week's time there were macrophages with little tendency to the formation of foreign body giant cells.

Several members of the dermatology service at the Veterans Administration Center in Los Angeles have employed gelfoam® in minor surgical procedures the past few years for its hemostatic effect. They have employed the agent in its dry state by cutting it down to the size of the wound and then inserting it into the depth of the surgical wound. Pressure was maintained on the sponge until it became adherent. Handling of the sponge was done under aseptic measures, and fresh gelfoam® was utilized. The histopathologic picture of the sponge in its various stages of absorption presents an interesting microscopic observation which to the uninitiated may prove to be a baffling situation. In the following cases certain features of the cutaneous histopathologic reactions observed were illustrated.

REPORT OF CASES

CASE 1.—W. A. C., a 58 year old white man, had an epidermoid cyst removed from his back, at which time gelfoam® was packed into the wound. This area was excised eight days after insertion of the gelfoam® and two days after the death of the patient.

CASE 2.—D. C. M., an 80 year old white man, had a specimen removed for biopsy of a basal cell carcinoma of the face, at which time gelfoam® was packed into the wound. This area was excised 21 days after insertion of the gelfoam.®

CASE 3.—O. M., a 60 year old white man, had a biopsy performed on a squamous cell carcinoma of the dorsum of the left hand, at which time gelfoam® was packed into the wound. This area was excised 28 days after insertion of the gelfoam.®

CASE 4.—A. M., a 56 year old white man, with seborrheic dermatitis of the anterior chest wall, had a biopsy specimen removed, at which time gelfoam® was packed into the wound. This area was excised 119 days after insertion of the gelfoam.®

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4. Pilcher, C., and Meacham, W. F.: Absorbable Gelatin Sponge and Thrombin for Hemostasis in Neurosurgery: Experimental and Clinical Observations, Surg., Gynec. & Obst. **81**:365-369 (Oct.) 1945.

5. Jenkins, H. P., and Clarke, J. S.: Gelatin Sponge: A New Hemostatic Substance; Studies on Absorbability, Arch. Surg. **51**:253-261 (Nov.-Dec.) 1945.

DISCUSSION

At the time of death the gelfoam® in case 1 had been present at the site of excision of the epidermoid cyst for eight days. Serial sections revealed a sinus tract leading to the skin surface and draining a large area of subepidermal abscess formation. No gelfoam® could be found within the walls of the abscess or its adjacent tissue. However, small fragments of relatively intact unaltered gelfoam® were found floating freely within the purulent lake of the abscess cavity. The picture in no

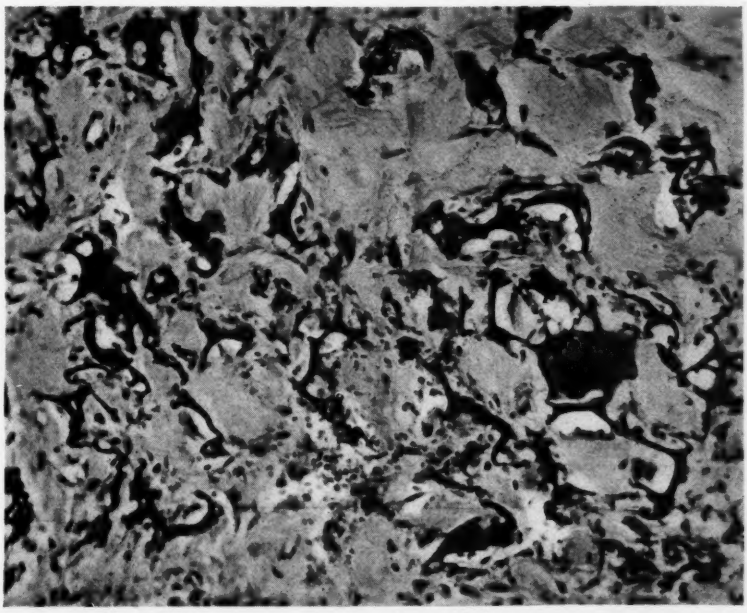


Fig. 1 (case 2).—Note how gelfoam® strands branch and exhibit shrinkage with creation of space artefacts. About these strands are occasional lymphocytes, eosinophilic and neutrophilic polymorphonuclear leukocytes and histiocytes. The latter may contain cytoplasmic hemosiderin granules. The fibrillar anuclear interstitial connective tissue is illustrated; hematoxylin and eosin, × 195.

way represented a reaction to gelfoam® but merely illustrated the appearance of unaltered gelfoam® bathed by a purulent exudate.

The gelfoam® in case 2 had been present for 21 days at the time of excision. The typical irregular branching and bridging (blue hematoxylin-stained) gelfoam® was found deeply situated within the scarified subepidermal tissues at the biopsy site. To one side was found the suture foreign body granuloma, and to the other, residua of the basal cell carcinoma (adnexal in origin). Isolated fragments of gelfoam® and matted clumps of gelfoam® induced the same reaction, and the intensity

of the reactive process appeared to be proportional to the amount of gelfoam® present. The gelfoam® strands had for the most part retracted away from the stroma of the reaction, producing space artefacts. The gelfoam® was uniformly homogeneous and stained a range of blue from sky to navy blue. Only when dissolution of the gelfoam® occurred did one encounter specific changes within this substance. Two methods of dissolution were identified. The commonest was characterized by a gradual fine blue granular change in the homogeneous ground substance (its blue

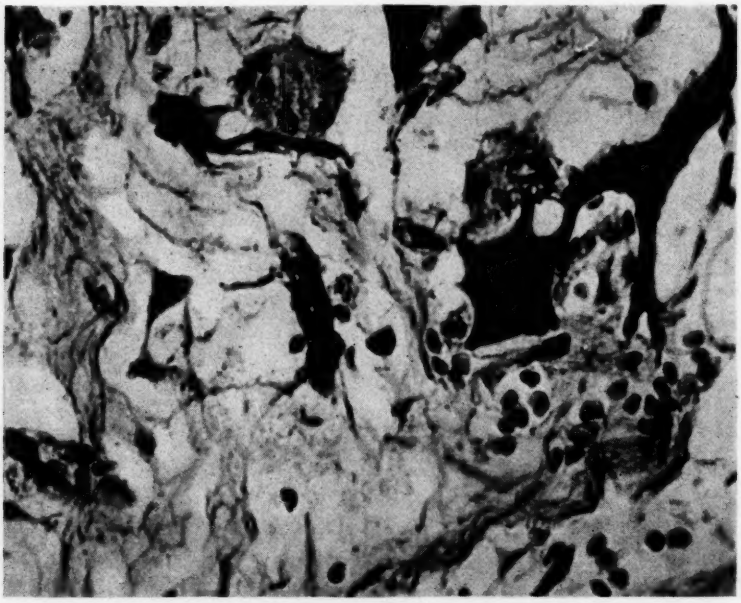


Fig. 2 (case 2).—Note the multinucleated histiocytes, one of which contains phagocytosed gelfoam®; hematoxylin and eosin, × 475.

color lightened) with what appeared to be a gradual solution of the strands peripherally. The least common absorptive process was characterized by fibrillation and phagocytosis within multinucleate histiocytes. About the gelfoam® masses and between the fibers there were relatively anuclear fibrillar bands of pink collagen. Immediately adjacent to the gelfoam® strands were found occasional lymphocytes, eosinophilic polymorphonuclear leukocytes and uninucleated and occasional multinucleated histiocytes. Many of the uninucleated histiocytes contained large amounts of intracytoplasmic hemosiderin granules. Fibroblasts, endotheliocytes and capillary channels were found growing loosely against and along the gelfoam® strands (figs. 1 and 2).

At the time of excision the gelfoam® had been present within the original biopsy site in case 3 for 28 days. The biopsy site itself was coated by a thick crusted exudate and cellular debris. Beneath this was found a broad zone denuded of epithelium and consisting of rich cellular granulation tissue containing chronic inflammatory cells and numerous foreign body granulomas. Into the overlying thick crust had been extruded and incorporated a considerable amount of pale-blue-staining gelfoam.® At one edge of this epithelial discontinuity was found a

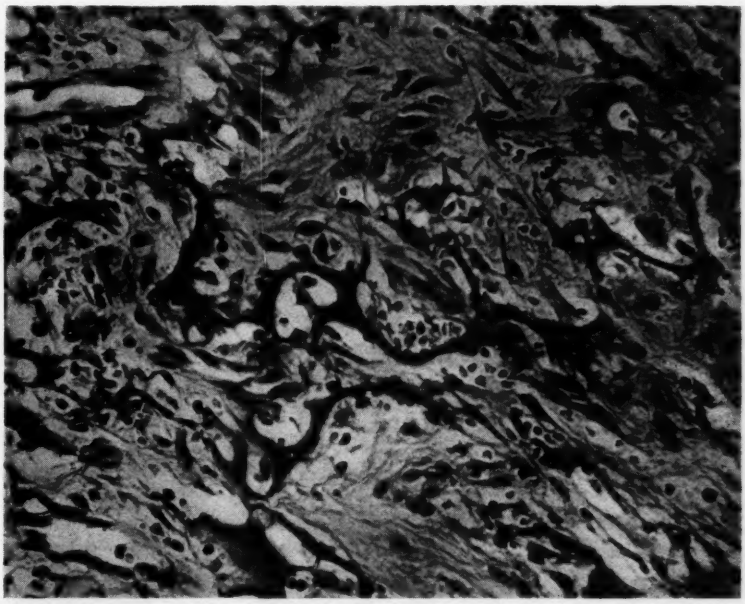


Fig. 3 (case 3).—Note the fibroblastic activity and the newly formed capillaries adjacent to the gelfoam® strands; hematoxylin and eosin, × 300.

subepidermally located area containing gelfoam.® This was immediately subjacent to the ulcer margin, where active squamous epithelial regeneration was observed. The gelfoam® presented essentially the same staining characteristics and morphologic pattern seen in case 2. Between these gelfoam® bands were found actively proliferating fibroblasts, endotheliocytes and occasionally relatively anuclear compact bands of fibrillar pink collagen. Newly formed blood capillaries were found situated adjacent to the gelfoam® bands, separating these from the proliferating fibroblastic collagen-producing tissue.

The apparent activity of the fixed tissue response at the site of gelfoam® was no doubt related to the persistent ulceration and nonspecific chronic inflammation resulting therefrom. This reaction was in sharp contrast to the relatively quiescent deposition of collagen seen in case 2.

The gelfoam® in case 4 had been in place for 119 days before removal. The epidermis and superficial subepidermal tissues showed the anatomic changes of a nonspecific dermatitis. Just beneath this was observed a

Fig. 4 (case 3).—Note smudgy gelfoam® strands in crust overlying persistent ulcer at the biopsy site; hematoxylin and eosin, × 80.

roughly circular nondemarcated area of pink-staining dense collagenous connective tissue that peripherally faded gradually into the normal spongy arrangement of subepidermal connective tissue. The dense collagenous bundles, centrally within this area, were of variable thickness, compact, finely fibrillar and practically anuclear. The collagen bundles whorled slightly and were separated only enough to permit the penetration of delicate capillary channels. No gelfoam® could be identified in serial sections of this scar, though minute finely particulate granules of blue could be found here and there amidst the collagen bundles.

SUMMARY

Four cases illustrating certain features of the cutaneous histopathologic reactions to gelfoam® are reported. In the first gelfoam® bathed in purulent material was exhibited. In the second a sterile scarifying reaction to gelfoam® was illustrated. In the third the fixed tissue reaction to gelfoam® accompanied with a nonspecific inflammatory reaction was shown. In the fourth case the end phase of the reactive process, the deposition of acellular fibrous connective tissue at the site of gelfoam® deposits, was demonstrated.

Clinical Notes

LYMPHADENOSIS CUTIS CIRCUMSCRIPTA TREATED WITH RADIOACTIVE PHOSPHORUS

SETH S. BARNES, M.D.
AND
THOMAS W. MOFFATT, M.D.
ST. LOUIS

Lesions of leukemia cutis occur more frequently in lymphogenous leukemia than in myelogenous or monocytic leukemia. Cutaneous lesions may be present in the acute, chronic and so-called aleukemic phases.[1] There is much variation in their size, number, distribution and other characteristics. In lymphogenous leukemia the cutaneous lesions have been observed to appear and disappear consistently with the fluctuations in the white blood cell count[2]; on the other hand, a case has been cited in which the cutaneous tumors continued to appear and became pronounced despite the fall of the white blood cell count to normal ranges. The tumors are usually sensitive to radiation.

Although the appearance of tumors is usually considered of grave prognostic import, many occur from one to several years before death. They are prone to occur about the head. Cleland[3] has expressed the opinion that local infiltrations are metastases, and he called attention to a case in which sites of injections and surgical incisions became infiltrated with leukemic tissue.

Schmidt,[4] in 1931, said there have been only a few reports in the literature on lymphogenous leukemia of the skin which were supported by histologic evidence. On the other hand, Gates[5] in 1938 stated that leukemia cutis occurs so frequently as to excite little interest. From our survey of the literature we are impressed by features of our own case that appear to be unique. We could find in the literature no report of the treatment of lymphadenosis cutis circumscripta by means of radioactive phosphorus.

Dr. Barnes and Dr. Moffat are fellows in Dermatology, Barnes Hospital and the School of Medicine, Washington University.

Studies, observations and reports from the Department of Dermatology of The Barnard Free Skin and Cancer Hospital and the School of Medicine, Washington University, St. Louis, Mo., service of Dr. Richard S. Weiss.

1. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 7, Philadelphia, Lea & Febiger, 1948, p. 868.

2. Butler, J.: Lymphatic Leukemia with Primary Manifestations of the Skin, Arch. Dermat. & Syph. **2**:594-606 (Nov.) 1920.

3. Cleland, cited by Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 788.

4. Schmidt, F. R.: Leukemia Cutis: Report of Case, Arch. Dermat. & Syph. **24**:587-590 (Oct.) 1931.

5. Gates, O.: Cutaneous Tumors in Leukemia and Lymphoma, Arch. Dermat. & Syph. **37**:1015-1030 (June) 1938.

REPORT OF CASE

M. L. B., a 52 year old housewife, presented herself to the dermatologic service of the Washington University Clinics on Aug. 23, 1948 Her complaint was disfigurement from a "spot" that had made its appearance in the skin of the bridge of the nose one year previously and slowly increased in size until its presence had become conspicuous. She had first visited Washington University Clinics in July 1946. After work-ups in the otolaryngology and medicine clinics she was hospitalized in Barnes Hospital on July 23, 1946. At the time her complaints were enlarged cervical nodes, increasing weakness, loss of weight, palpitation, shortness of breath on exertion and mild swelling of both feet and ankles, all of three to six months' duration. She had no knowledge of blood dyscrasia in her family history. She

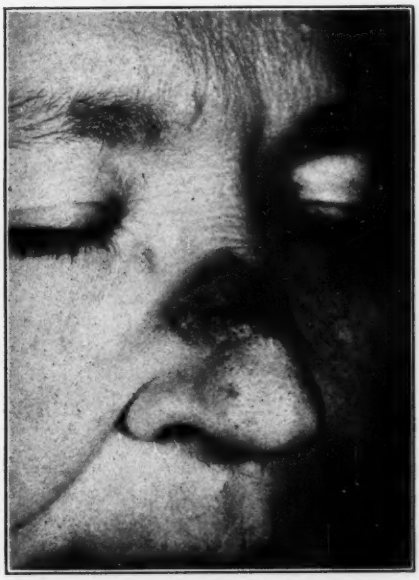


Fig. 1.—Lesion of lymphadenosis cutis circumscripta on the bridge of the nose.

gave a past history of rheumatic fever in 1939 and severe pneumonia in December 1945 with failure to regain strength.

Examination at that time revealed an intelligent white housewife of medium stature with many signs of chronic illness. Her skin showed a deep pallor. Multiple minute depigmented areas were scattered over her retinas and in her left fundus there was a rectangular hemorrhagic area with a raised spot in the center. There was enlargement of the cervical and axillary lymph nodes; her spleen was down to the iliac crest and the lower border of the liver was 3 fingerbreadths below the right costal border.

Hematologic examination revealed 3,160,000 red cells, 9 Gm. of hemoglobin and 224,000 white cells, with a differential count of 1 per cent eosinophils, 2 per cent segmented granulocytes and 97 per cent lymphocytes. The sternal bone marrow count was 1 eosinophil, 2 segmented polymorphonuclear cells, 94 lymphocytes, 1

myelocyte and 1 band cell per hundred cells. There were 3 normoblasts and 1 erythroblast (a total of 4 red cells) to each hundred white cells. Results of repeated urinalyses were normal, and the Kahn reaction of the blood was negative.

Treatment and Course.—After diagnostic studies had been completed, the patient was given roentgen radiation to the cervical nodes, axillary nodes and the spleen. The daily dosage was 200 to 400 r delivered with the following technical factors: 150 kilovolts, 16 milliamperes, 50 cm. target-skin distance, a 100 to 150 sq. cm. portal and 0.5 mm. of copper or 1 mm. of aluminum filtration. On five suc-

Fig. 2.—Lymphadenosis cutis circumscripta, low power magnification.

cessive days the right cervical, left cervical, right axillary, left axillary and splenic regions were irradiated in the order named. After a three day rest the same procedure was repeated. Four blood transfusions of 500 cc. each were given. Much improved, the patient was discharged from the hospital on August 16. During the following twenty months there was little change in her general condition. The next item of interest to us was the appearance of the plum-colored plaque on the bridge of the nose about July 1947. On April 27, 1948, she was hospitalized the second time, with pneumonia. The pneumonia responded well to penicillin. While in the

hospital she was given three more roentgen ray treatments over the spleen. This consisted in three successive daily irradiations of 150 r each (200 kilovolts, 16 milliamperes, 50 cm. target-skin distance, a 100 to 150 sq. cm. portal and 0.5 mm. of copper or 1 mm. of aluminum filtration). Two more 500 cc. blood transfusions were administered. On May 15 she was again discharged. Approximately three months after the second hospitalization she was referred to the dermatology department for diagnosis of the expanding skin lesion.

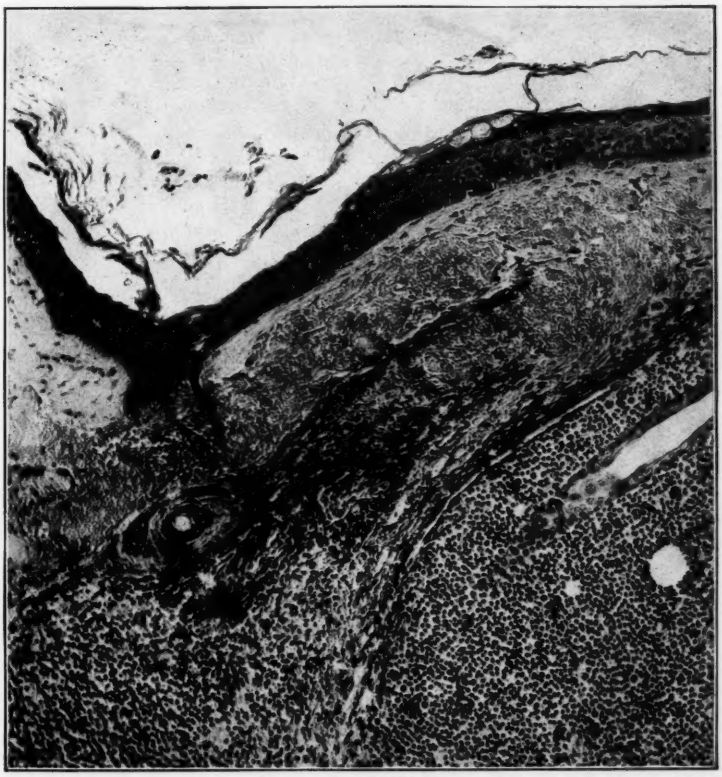


Fig. 3.—Lymphadenosis cutis circumscripta, high power magnification.

Description of Skin Lesion.—Located with its longest dimension crossing the midline of the bridge of the nose was a prominent pigmented skin plaque (fig. 1). The surface of the plaque was rough and slightly elevated. The borders of the lesion were irregularly rectangular; the lesion measured 2 by 3 cm. Close inspection revealed the lesion to consist of a network of papules 2 to 5 mm. in diameter. On diascopic pressure these papules assumed a brownish yellow hue resembling apple jelly nodules. When grasped in the finger tips, the papular network felt loose, doughy and elastic and was nonadherent to the underlying tissues.

A biopsy of the skin plaque was obtained September 9. The epidermis was regularly thinned out, with obliteration of the rete ridges in the central portion of the specimen (fig. 2). The epidermal cells appeared normal. The basal cell layer was everywhere intact, and the basal cells contained a uniformly distributed golden brown, granular pigment in their cytoplasm.

The cells themselves were primarily of the lymphocytic series and represented all stages of maturity of this series of cells (fig. 3). There was a fairly high

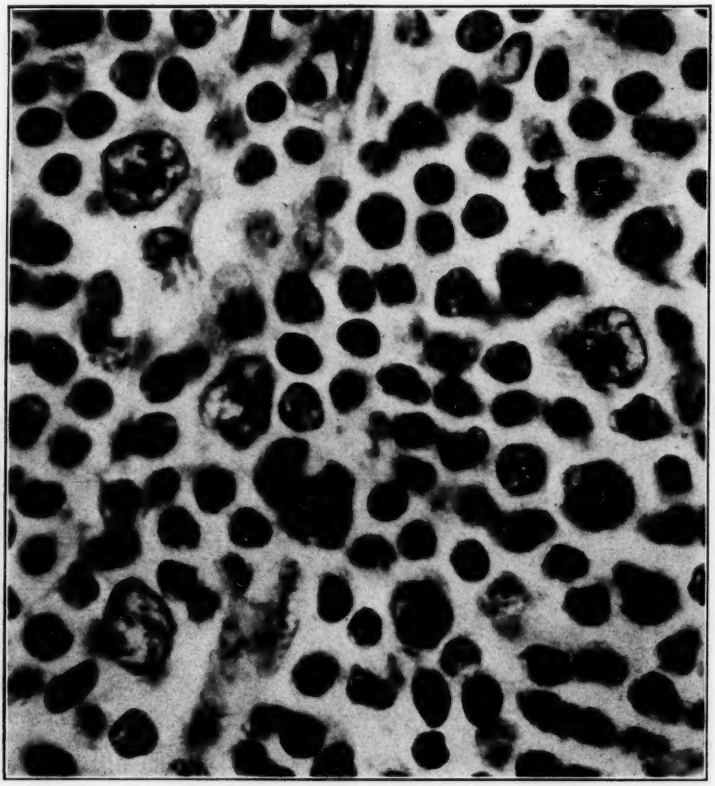


Fig. 4.—Photomicrograph of lymphadenosis cutis circumscripta, oil immersion.

proportion of extremely large cells with vesicular, irregular nuclei and scanty, somewhat basophilic cytoplasm. These larger cells were occasionally binucleate and characteristically contained a very large, brilliantly red nucleolus. Occasional rosettes of mononuclear cells were seen whose chromatin appeared to be blocked rather heavily around the periphery of the cell. These cells exhibited a fairly abundant basophilic cytoplasm in which the nucleus was eccentrically located. There were several arterioles whose lumens were completely filled with a similar type of mononuclear cells (fig. 4). Occasional strands of compressed fibrous con-

nective tissue could be seen, but, by and large, there was a minimal amount of stroma in the cellular infiltrate. One or two compressed sebaceous glands could be seen in association with some badly distorted hair follicles.

Treatment with Radioactive Phosphorus and Subsequent Course.—Since the biopsy the patient has received additional radiation therapy in the form of radioactive phosphorus. On October 14 she was given 3.27 millicuries of P^{32} by intravenous injection of a soluble phosphorus salt. There was evidence of improvement within a few weeks, and on November 22 a second injection of 1.09 millicuries was given. On December 20 she reported back for her check-up, had gained 5 pounds (2.3 Kg.) and felt considerably better than before treatment with radioactive phosphorus. The lymph nodes, spleen and liver had diminished in size and the leukocyte count had dropped to 15,500. On Jan. 17, 1949, when last seen, she was still gaining in strength and weight; however, it was noted that the skin plaque had failed to regress. The surface of the plaque was more uneven and more elevated. The borders now measured 2.5 by 4 cm. The individual papules in the lesion were more numerous than before, and the larger ones measured up to 1 cm. in diameter. The lesion by this time formed a lumpy, plum-jelly-like mass with a stuck-on appearance covering more than half of the nasal skin.

SUMMARY

A case is reported in which a solitary nodular skin plaque developed on the bridge of the nose of a 52 year old housewife with chronic lymphogenous leukemia. Biopsy findings were consistent with the clinical diagnosis of lymphadenosis cutis circumscripta.

Though treatment with radioactive phosphorus effected an excellent clinical improvement in the patient, the lymphadenosis cutis circumscripta failed to regress after the injection of P^{32}. On the contrary, there was a measurable increase in the size and number of the individual papules forming the plaque.

PRACTICAL METHOD FOR APPLICATION OF GELATIN SPONGE (GELFOAM®) TO A BIOPSY WELL

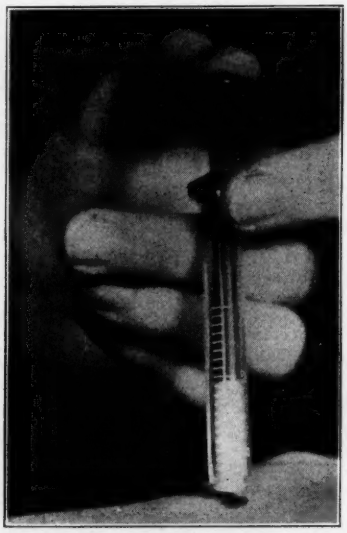
JAMES H. McCREARY, M.D.
CHICAGO

Gelatin sponge (gelfoam®) has proved to be effective in controlling the bleeding from punch biopsy wells, but its application is sometimes clumsy and time consuming. When introducing the gelatin sponge into a biopsy well by the use of tissue forceps, the sponge is often pulled out as the forceps is withdrawn. Usually, when this happens a new sponge must be inserted, because the first sponge has become so saturated with blood that it no longer will pack sufficiently to accomplish hemostasis. In the meantime, the bleeding has continued, especially if the biopsy site happens to be a vascular one. The use of a glass injector, as shown in the accompanying photograph, permits the operator to apply the sponge directly into the well without loss of too much time or motion.

From the Section of Dermatology and Syphilology, Department of Medicine, University of Chicago.

In the preparation for the taking of a biopsy specimen, the injector is sterilized by boiling and allowed to dry. The sponge is cut from strips in the original container and packed into the cylinder by using sterile scissors and forceps. Immediately after the removal of the tissue for biopsy, the sponge is packed firmly into the well by pressure on the injector plunger. The injector is then held in place for a few seconds to allow a clot to form through the sponge. This leaves a dry, well sealed and sterile biopsy wound.

The injector can be made easily by filing off the ends of the cylinder and plunger of an ordinary tuberculin syringe. The rough ends can be matched and smoothed by emery paper. A tuberculin syringe is adequate for smaller biopsy



Glass injector.

wells. Larger syringes can be modified similarly for biopsies of greater diameter. Disposable plastic injectors of varied diameters could be manufactured.

COINCIDENCE OF PITYRIASIS ROSEA WITH PREGNANCY

EDWARD F. CORSON, M.D.
and
HERBERT A. LUSCOMBE, M.D.
PHILADELPHIA

The observation by one of us (E. F. C.) of 3 instances of pityriasis rosea in pregnant women during a period of two weeks caused us to be on the lookout for such coincidences. All cases of pityriasis rosea in women of the ages 17 to 48 years inclusive were investigated from this standpoint. The nonpregnant patients

were often single women, while those who were pregnant were all married. The cases were observed in the private practice of one of us (E. F. C.) and at the skin dispensary of the Jefferson Medical College Hospital.

Two patients whose cases were included among those arising during pregnancy were first seen during the week following delivery, and it was pretty clearly evident that the outbreak had been present and unrecognized before childbirth. In the table their outbreak is listed as starting in the ninth month of pregnancy.

All cases recorded were typical examples of pityriasis rosea, the diagnosis of the dispensary cases being agreed on by two or more staff members, while the existence of pregnancy in all instances was confirmed by obstetricians.

Between Feb. 6, 1944 and Oct. 1, 1948, 10 private patients were observed to exhibit the rash of pityriasis rosea and were found to be pregnant, while 49 persons with pityriasis rosea who were of the age group mentioned, both married and single women, either were not demonstrably pregnant or denied being in that

Data Concerning Fourteen Cases of Pityriasis Rosea Arising During Pregnancy

Patient	Duration of Pregnancy, Months	Location of Herald Spot
V. P. S.	6½	Left arm
B. S. L.	6	Inner aspect of right thigh
M. C.	9	Left breast
M. K.	8	Right flank
H. C. G.	7	N. R.
W. L. D.	9	Left flank
H. R.	3	Left side of neck
M. B.	3½	N. R.
G. W. M.	5	N. R.
D. M. G.	7	Right flank
E. F.	6½	N. R.
B. L. W.	3	N. R.
L. B.	7	N. R.
M. J.	5	N. R.

N. R. indicates that the herald spot was either not recognized as such or not recorded on the history sheet. Multiple initial foci would be so marked.

condition. Between Oct. 1, 1946, and Oct. 1, 1948, 4 dispensary patients with pityriasis rosea were pregnant, while 13 were not pregnant as far as could be ascertained. Of this total of 76 patients 14, or over 18 per cent, were pregnant. To verify our impression that this was a surprisingly high coincidence of pityriasis rosea with pregnancy among our patients, we listed 100 consecutive cases of a variety of common skin diseases other than pityriasis rosea among women of the same age group and found 6 per cent of the patients to be pregnant. In the last-mentioned group was a cross section of the usual run of common skin diseases.

In the accompanying table it may be noted that only 3 cases are set down as occurring in the first half of pregnancy. The location of a herald spot was not always recorded on the histories; in some instances that lesion could not be positively identified.

COMMENT

On what grounds can the high incidence of this dermatosis in pregnancy be explained? The influence of new clothing as an etiologic agent has received attention for many years. It is a common habit among women to provide new raiment for their swelling bodies—maternity belts, breast supports, underwear and so-called

"outer" dresses which nevertheless frequently contact the skin in various regions. It is possible that during the time of gestation more new clothing is procured and worn than at any other equal period of a woman's life. In our ignorance of the true cause of pityriasis rosea we can only point to suggestive factors. New clothing may be the bearer of the responsible agent. In approximately 70 per cent of our cases, there was a history of contact with new clothing.[1]

Again, during pregnancy there is increased secretory activity in virtually all the glands of the body. On the surface sebaceous and sweat secretions are poured out in greater quantity than usual. To avoid odors the patient must bathe more frequently. Tinea versicolor is more likely to develop. Other diseases of the skin are commoner during pregnancy.[2]

The ductless glands are amply proved to become hypertrophied and to increase their products. Could it be possible that hormones play a part in producing the outbreak by rendering the skin a better seed bed for some infectious material? Among the 49 nonpregnant private patients recorded, there was 1 who blamed her rash on the hormonal injections she was receiving. However, she had recently purchased a new brassiere, and the herald spot was directly under its strap.

SUMMARY

In women of childbearing age we found a higher incidence of pityriasis rosea among those who were pregnant.

Medical Arts Building.

Jefferson Hospital.

1. Epstein, S.: Etiology of Pityriasis Rosea, Urol. & Cutan. Rev. **47**:641, 1943. Veiel, F.: Zur Kenntnis der Pityriasis rosea, Dermat. Ztschr. **62**:91, 1931; abstracted, Wise, F.; Sulzberger, M. B., and Cunningham, J. H.: Practical Medicine Series, Chicago, The Year Book Publishers, Inc., 1931. Butterworth, T.: Pityriasis Rosea: Clinical Varieties and Etiology, Pennsylvania M. J. **38**:400, 1935.

2. DeLee, J. B., and Greenhill, J. P.: Principles and Practice of Obstetrics, ed. 9, Philadelphia, W. B. Saunders Company, 1947.

TURNER'S SYNDROME ASSOCIATED WITH LICHEN PLANUS

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JAMES R. WEBSTER, M.D.
AND
DONALD P. MUSGRAVE, M.D.
CHICAGO

Turner[1] first described a curious syndrome, observed in 7 female patients, consisting of webbing of the neck, cubitus valgus and infantilism. Sharpey-Schafer[2] added a case, also in a female patient, of this triad and described the postmortem observations.

From the Department of Dermatology, Cook County Hospital.

1. Turner, H. H.: A Syndrome of Infantilism, Congenital Webbed Neck, and Cubitus Valgus, Endocrinology **23**:566, 1938.

2. Sharpey-Schafer, E. P.: A Case of Pterygo-Nuchal Infantilism, Lancet **2**:559, 1941.

Recognition of webbing of the neck dates from 1883, when Kobylinski [3] described it. Four cases were added by Frawley,[4] all in females. Webbing occurs in the Klippel-Feil syndrome, also, apparently a commoner variety, but it is associated with synostosis of the cervical vertebrae with limitation of motion, and there is no infantilism. By these characteristics the Klippel-Feil syndrome is easily differentiated from Turner's. The cause of webbing is not known, but it has been thought to result from amniotic bands, to be a form of atavism or to be a developmental defect dating from the third month of fetal life, when the shoulders and head are in lateral alinement.

Although Turner expressed the opinion that his syndrome had a connection with the anterior lobe of the pituitary gland, Sharpey-Schafer adduced evidence that there is a primary gonadal defect. Postmortem examination of his patient showed the various endocrine glands, including the pituitary, to be normal in appearance. There was, however, no functioning ovarian tissue that could be seen by histological examination.

REPORT OF A CASE

A Negro woman 24 years old had had a normal childhood development but had always been short for her age. There had been no secondary sexual development, and she had never menstruated. The family history was noncontributory, except that the paternal grandmother was of very short stature too. Mental development was normal. Physical examination showed her height to be 50 inches (127 cm.) and her weight, 77½ pounds (35 Kg.). The hair line was low anteriorly and posteriorly. The head was normal. Nothing abnormal was seen in the oral examination. There was an extension of the skin of the neck to form a triangular winged appearance that extended symmetrically on both sides from the mastoid process to the acromion. There was nothing abnormal about the texture or appearance of the skin itself. The extension seemed not to include any subjacent structures, such as muscle. It gave rise to neither pain nor tenderness when the head and neck were stationary or in movement. The neck was free in all directions and had normal rotation. The breasts were of male type, and the chest showed a somewhat barreling effect. There was no visible axillary hair. The upper extremities were carried with the elbows at an increased angle. The ring finger of each hand was the same length as the little finger. The pubic hair was lacking, and the vulva was infantile. The gynecologist found that the vagina was rudimentary and admitted one finger. No uterus or ovaries could be palpated through the rectum.

There was a generalized pruritic lichenoid eruption most pronounced over the back, buttocks, chest and abdomen. The lesions were flat topped and burnished with scaling visible where the papules had coalesced into patches. The face, palms and soles were uninvolved.

The laboratory examination of the urine and blood showed nothing abnormal. The total cholesterol was 250 mg. per hundred cubic centimeters, and the basal metabolic rate was 10 per cent. Roentgenologic examination of the chest and cervical portion of the spine showed them to be normal. A similar examination of the hands and wrists found a bilateral shortening of the fourth metacarpal bone

3. Kobylinski, O.: Ueber eine flughautähnliche Ausbreitung am Halse, Arch. f. Anthrop. **14**:343, 1883.

4. Frawley, J. M.: Congenital Webbing, Am. J. Dis. Child. **29**:799 (June) 1925.

Fig. 1.—Lichen planus; low power magnification.

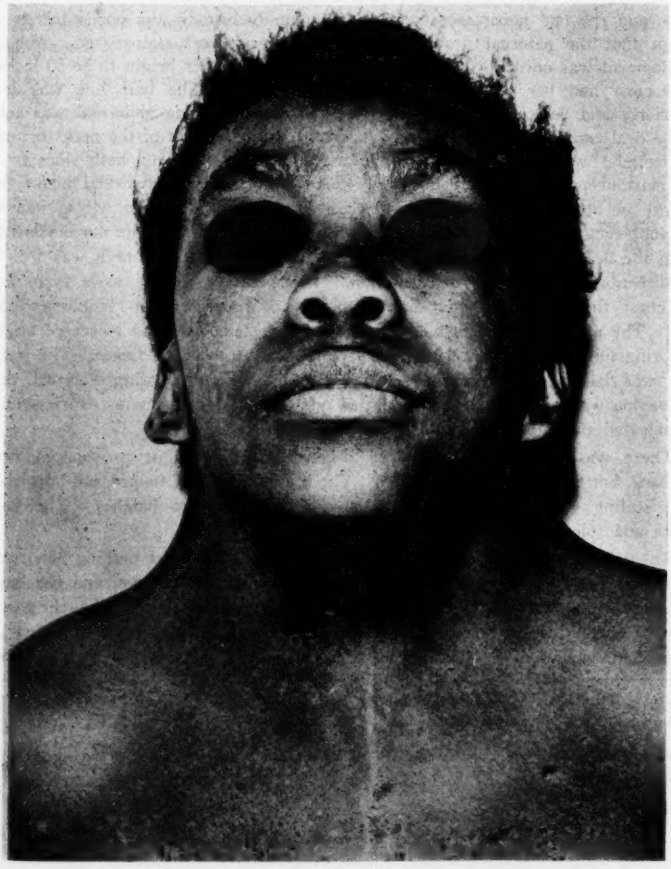

Fig. 2.—A close-up view, showing webbing of the neck.

with delayed epiphysial closures of the bones of the hands and wrists. There was, likewise, shortening of the left fourth metatarsal bone. Histological examination of the involved skin showed changes compatible with a diagnosis of lichen planus. A twenty-four hour sample of urine was assayed for 17-ketosteroids and estrogens. There was 6 mg. of the former in terms of 17-ketoandrosterone and none of the latter.

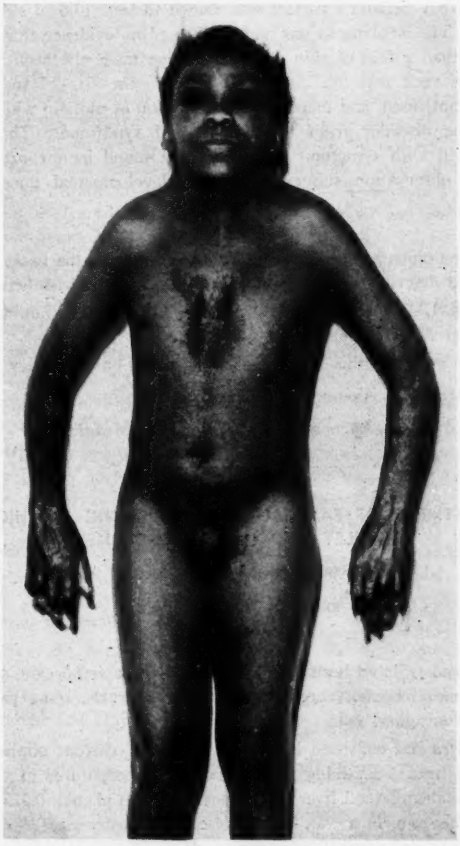

Fig. 3.—General appearance of the patient; webbing, cubitus valgus, undeveloped secondary sex characteristics and eruption of lichen planus may be observed.

COMMENT

In 1 of Turner's original cases there were numerous nevi present, but he did not mention any changes in the skin of his other 6 subjects. In Sharpey-Schafer's patient, too, there were numerous nevi. In our patient there was an extensive eruption of lichen planus but no remarkable nevus formations.

The triad characteristic of Turner's case was present in our patient, namely, webbing of the neck, cubitus valgus and infantilism. The evidence in Sharpey-

Schafer's case was decisive for a primary ovarian defect. In our patient, the presence of a normal amount of 17-ketosteroids but absence of estrogens spoke also in favor of a primary ovarian defect. The dwarfism is to be differentiated from the Lorain-Levi variety, in which the anterior lobe of the pituitary gland is to blame. Our patient, like that of Sharpey-Schafer, had no axillary hair and practically no hair over the pubis but normal development of scalp hair. The webbing in Sharpey-Schafer's patient was shown to be a fold of skin only, enclosing no muscle. The webbing in our patient showed no evidence that it consisted of anything more than a fold of skin. This condition made the neck appear shorter, but actually the neck was not disproportionate to the size of the patient. The vertebrae were not fused, and there was no limitation of motion, which observations distinguished the disorder from the Klippel-Feil syndrome. Thus far, all the subjects described with symptoms similar to that found in our patient have been females. This observation suggests that the developmental anomalies are sex linked.

SUMMARY

A patient (the ninth in the literature) with webbing of the neck, cubitus valgus and infantilism is described. This syndrome was associated with lichen planus.

The urinary 17-ketosteroids were of normal quantity, but there were no estrogens recovered from the urine.

The evidence points to this syndrome as one based on a primary ovarian defect.

30 North Michigan Avenue (Dr. Cornbleet).

122 South Michigan Avenue (Drs. Webster and Musgrave).

TREATMENT OF FAMILIAL BENIGN CHRONIC PEMPHIGUS (HAILEY AND HAILEY SYNDROME)

Rapid Healing with Aureomycin

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NEWARK, N. J.

Numerous reports have been published in the past few years, concerning the treatment of familial benign chronic pemphigus. For the most part, these have been rather discouraging.

Local treatment has consisted in the application of various ointments, including daxalan® (an ointment containing whole crude tar, incorporated in a special hydrophilic base), gadoment® (cod liver oil, 70 per cent, and phenol, 0.375 per cent, with zinc oxide and benzoin, in a wax base), desoxycorticosterone (20 mg. per 100 cc. of ointment base [1]) and penicillin ointment. Also superficial roentgen ray therapy has been employed. Internal treatment has consisted in the administration of vitamin A in large doses.[2] Injections of oxophenarsine hydrochloride (mapharsen®), oral administration of sulfapyridine, penicillin injections, autogenous vaccines, intravenous injection of Staphylococcus aureus vaccine combined with low power

1. Lewis, G. M.: Disseminated Bullous Dyskeratoid Dermatosis (Benign Familial Pemphigus), Arch. Dermat. & Syph. **57**:499 (March, pt. 2) 1948.

2. Pinkus, A., and Epstein, S.: Familial Benign Chronic Pemphigus, Arch. Dermat. & Syph. **53**:119 (Feb.) 1946.

roentgen therapy and also staphylococcus toxoid injections have been tried.[3] All these have met with varying degrees of success in some, and failed to produce any response in others.

As this eruption has been frequently considered to be a form of dermatitis herpetiformis [4] and since aureomycin has reportedly given such excellent results in dermatitis herpetiformis, I thought that aureomycin might be worthy of a trial in this case.

REPORT OF A CASE

H. O., a white woman aged 42, first came under my care in May 1941 for treatment of an eruption on both sides of the neck. She was given superficial roentgen ray therapy, together with an ointment consisting of 3 per cent crude coal tar. The lesions cleared in about six weeks. I did not see the patient again until August 1942, when she had a recurrence on both sides of the neck, in the right axilla and on the medial side of the left thigh. Treatment was repeated, and the condition again cleared in two months. The patient had various recurrences for the next five years, with remissions lasting from one to six months. With each recurrence she was given sulfapyridine by mouth with very effective results. From June 1946 until October 1947 she was treated for this condition by an internist by means of various hormones, without effect. She returned in October 1947 with both sides of the neck involved. The skin was macerated, and there had developed a superimposed dermatitis from local preparations. In October 1947, since she could no longer take sulfapyridine because of its effect on the stomach, she was given vitamin A in doses of 150,000 units daily for a period of three months without effect.

Oral administration of bismuth sodium triglycollamate (bistrimate,® each tablet representing 75 mg. of metallic bismuth) was then begun but had to be discontinued at the end of two weeks because of continued nausea. The patient was then given a series of injections of stibophen (fuadin®) without effect.

She was then given a salve consisting of 20 mg. of desoxycorticosterone acetate in 100 cc. of a hydrophilic base simultaneously with oral administration of ascorbic acid (1,000 mg. per day).[1] This treatment was continued for one month without any appreciable improvement.

In September 1948 biopsies were taken from the neck, the right axilla and the medial side of the left thigh and were sent to Dr. Fred Weidman at the University of Pennsylvania for examination. Dr. Weidman concurred with the diagnosis of Hailey and Hailey syndrome. The section from the side of the neck showed the typical lacunas, lined by cells in various stages of dyskeratosis. The epidermis was acanthotic. All the cells showed a pronounced spongiosis. In the papillae and the subpapillary region there was a diffuse inflammatory infiltration with numerous polymorphonuclear cells present. In short, the picture was that of Hailey and Hailey syndrome but with a superimposed and highly edematous dermatitis in the order of an eczematoid reaction.

The specimen taken from the axilla showed the typical lacunas, lined by cells in an early stage of dyskeratosis. The epidermis was highly acanthotic. The surface was strongly verrucous and covered by a thick layer of purely hyper-

3. Carpenter, C. C.: Treatment of Familial Benign Chronic Pemphigus: Rapid Improvement with Penicillin Therapy, Arch. Dermat. & Syph. **58**:80 (July) 1948.

4. Ayres, S., Jr., and Anderson, W. P.: Recurrent Herpetiform Dermatitis Repens, Arch. Dermat. & Syph. **40**:402 (Sept.) 1939.

keratotic material; there was no parakeratosis. The basal cells were hyperpigmented, and a few small aggregations of chromatophores were present (the lesion in the right axilla was deeply pigmented and verrucous and presented the clinical appearance of acanthosis nigricans).

The lesion on the medial side of the left thigh resembled lichen simplex chronicus or an atypical form of lichen planus. Dr. Weidman said that he was unable to advance a diagnosis of this lesion but stated that it was apparently not Hailey and Hailey syndrome and that lichen planus was reasonably excluded.

At this time the patient was seen in consultation with Dr. Marion Sulzberger, who suggested a course of intravenous injections of suramin (naphuride®) sodium. This was begun with small doses of 0.1 Gm. three times weekly in gradually increasing amounts. Blood pressure readings and complete blood counts and urine examinations were done weekly together with weekly blood determinations of the sodium, potassium, chloride and nonprotein nitrogen content in order that degeneration of the adrenal cortex might be detected early. During the administration of the suramin sodium all these remained within normal limits. When the patient had received 5.75 Gm. of the drug (which is about half the amount of what is considered to be a total maximum dose), she acquired generalized pruritus and the treatment had to be discontinued. There was no appreciable clinical improvement following these injections.

On Sept. 27, 1949, administration of aureomycin was begun in doses of 50 mg. every two hours (eight capsules, or 400 mg. daily). No local treatment was given. The patient was again seen one week later (October 5), when both sides of the neck were entirely healed. The lesion in the right axilla was 50 per cent improved.

The patient stated that healing began at the end of two days (after she had taken 400 mg.) and was complete at the end of four days (after 1,600 mg. had been taken).

Treatment is being continued, and the progress of the lesion of the right axilla is being noted.

SUMMARY AND CONCLUSIONS

It has been observed that local therapy has very little effect in the treatment of familial benign chronic pemphigus.

Oral administration of aureomycin is apparently the best treatment of this disease.

The frequent administration of small doses produces a satisfactory result and eliminates such side effects as nausea and diarrhea. The exact dosage and the period of administration necessary to prevent recurrences are yet to be determined.

NOTE.—Since this article was submitted, the patient has been seen periodically. She was kept on a maintenance dose of 200 mg. daily for two months. This was then reduced to 150 mg. daily and continued for another six months. During this period there were two slight recurrences which cleared within 24 hours on administration of 750 mg. aureomycin daily.

When the patient was last seen by us, on Sept. 6, 1950 (that is, one year after treatment with aureomycin was begun), all the lesions were entirely clear and had remained so for five months without medication.

After a year's observation, it has been found that the most satisfactory maintenance dose of aureomycin is 200 mg. daily.

23 Johnson Avenue.

CLINICAL EVALUATION OF A NEW PYROGENIC AGENT

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The value of nonspecific treatment, including pyretotherapy, in dermatology has long been recognized.[1]

The purpose of this communication is to report the results of a clinical trial of a new pyrogenic agent, pyromen.®[2] This substance is a purified product obtained from Pseudomonas aeruginosa. It is not a protein and is free from bacteria and other toxic material. It is not anaphylactogenic and is antigenic only in that increasing amounts usually must be given for each succeeding bout when repeated courses of fever are desired in a short period.[3]

After its intravenous administration a chilling phase ensues, during which there is peripheral vasoconstriction with concomitant decrease in the temperature of the skin of all the extremities. There is initial leukopenia followed by pronounced leukocytosis which usually persists for many hours. As with other forms of fever therapy, one occasionally encounters transient albuminuria and occasional hyaline casts.

Pyromen® has been successfully used in the treatment of neurosyphilis by Lonsen and Liebert,[4] who compared its action with that of malaria and typhoid vaccine.

SUMMARY OF STUDY

In this study, a total of 147 injections of pyromen® were given intravenously to 49 dermatologic patients, 36 of whom were males and 13, females. Their ages ranged from 14 to 60 years. Included in this group were 38 cases of the eczematous group of dermatoses, including neurodermatitis and atopic dermatitis, 5 cases of psoriasis, 2 of seborrheic dermatitis, 2 of acne, 1 of pityriasis rubra pilaris and 1 of congenital syphilis.

The usual initial dose was 25 micrograms (0.5 cc.) given intravenously, except for a few particularly debilitated patients, for whom smaller initial doses were used. The highest temperatures recorded after the initial injection were 102.2 F. from 15 micrograms, 102.8 from 20 micrograms and 102.4 from 25 micrograms. The greatest number of injections given any one patient was 10, and the highest dose given in any single injection in this study was 125 micrograms (2.5 cc.).

Generally the patient experienced a chill within 40 minutes to one hour following the injection and the peak elevation of temperature was achieved in two or 2½ hours. The duration of the height of the temperature elevation varied considerably between patients (extremes of three and 14 hours were recorded in different

*From the Section on Dermatology, Mayo Clinic.

1. O'Leary, P. A.: Present Status of Nonspecific Treatment in Dermatology, Arch. Dermat. & Syph. **15**:470-477 (April) 1927.

2. Supplied through the courtesy of N. M. Nesset, Ph.D., Baxter Laboratories, Morton Grove, Ill.

3. Nesset, N. M.: Personal communication to the authors.

4. Lonsen, W., and Liebert, E.: Studies on a New Pyrogen Fever Treatment, Illinois M. J. **96**:186-190 (Sept.) 1949.

patients), but it was found that in a given patient receiving a series of treatments the duration of the elevation of temperature was remarkably constant and, apparently, independent of the dose of the material injected.

The dosage which we found to be most satisfactory for our purposes was as follows: An initial dose of 25 micrograms (0.5 cc.) was given intravenously. Subsequent injections were given approximately every other day. If an oral temperature of 102 F. (which we feel is satisfactory) was achieved, the dose was kept the same or increased 20 to 30 per cent for the succeeding injection. If an unsatisfactory or insufficient response was elicited, the dose was increased 40 to 75 per cent, as indicated. If, for some reason, an interval of more than four or five days elapsed between injections, it was found advisable not to increase the dose, inasmuch as the patient had apparently recovered, to some extent, his original sensitivity to the pyrogenic agent used.

UNTOWARD REACTIONS

Most of the patients complained of mild headache with the first administration, but in none of the patients in this group did severe untoward reactions occur. Three of the patients complained of moderately severe headache.

It is interesting to note that one patient, a man 58 years old, complained of severe sharp pains in the hips and legs after the first injection. Subsequent investigation of this patient revealed the presence of bilateral femoral arteriosclerosis obliterans which had been asymptomatic and undiscovered hitherto.

CONCLUSIONS

Pyromen® is a safe agent for use in producing therapeutic fever. The results obtained with its use compare favorably with those of treatment with typhoid vaccine. We consider that it has advantages over typhoid vaccine in that the reaction produced can be modified to a desired degree by adjustment of the dose administered. The more unpleasant of the side effects so often seen with fever produced by typhoid vaccine appear to have been avoided.

Contraindications to the use of this agent are the same as for any other type of fever therapy.

LICHEN NITIDUS CONFINED TO THE FACE

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and
HENRY SCHORR, M.D.
CHICAGO

Since Pinkus [1] first described lichen nitidus in 1907 as occurring in men only, many cases have been recorded in both sexes and in different ages. Unusual features of this entity, such as its association with lichen planus and tuberculosis in some cases as well as its development in nonclassic areas, have continued to be reported.[2] This case is reported because of the unusual location of the lesions in a Negro girl.

1. Pinkus, F.: Ueber eine neue knötchenförmige Hauteruption: Lichen nitidus, Arch. f. Dermat. u. Syph. **85**:11, 1907.

2. Niles, H. D.: Lichen Nitidus, Arch. Dermat. & Syph. **22**:687 (Oct.) 1930. Wien, M. S., and Perlstein, M. O.: Lichen Nitidus, Arch. Dermat. & Syph. **30**:790 (Dec.) 1934.

REPORT OF A CASE

V. A., an 8 year old Negro girl, had an intermittent, nonpruritic, papular eruption of the face for about four years. The lesions disappeared completely each fall and recurred each spring. The eyes were "reddened" with each eruption. The mother said that the child had been otherwise well. There were no chronic skin diseases in the family. The patient's father had had pulmonary tuberculosis which had been arrested for five years. Results of the general physical examination were normal.

Fig. 1.—Lichen nitidus lesions occurring on the face.

There was a dense accumulation of skin-colored, uniform, pinhead-sized translucent papules involving the forehead, bridge of the nose, nasolabial areas and cheeks. The lesions were flat topped and not associated with the pilosebaceous apparatus. They yielded no fluid or cheesy material when pricked with a hypodermic needle. A mild bilateral conjunctivitis, which the ophthalmologist expressed the belief was due to the presence of papules on the eyelid margins, was present. The mouth appeared normal.

Nothing noteworthy was found by the urinalysis and the counts of the blood cells. The Wassermann reaction was negative. The chest appeared normal by

roentgenologic examination. The Mantoux test (0.1 cc. of 1:1,000 old tuberculin) gave a negative reaction. The report on the histologic examination by Dr. Marcus Caro was as follows:

"The epidermis was normal, and it contained considerable pigment in the basal layer except at the site of the lesion. In this small area, about the opening of

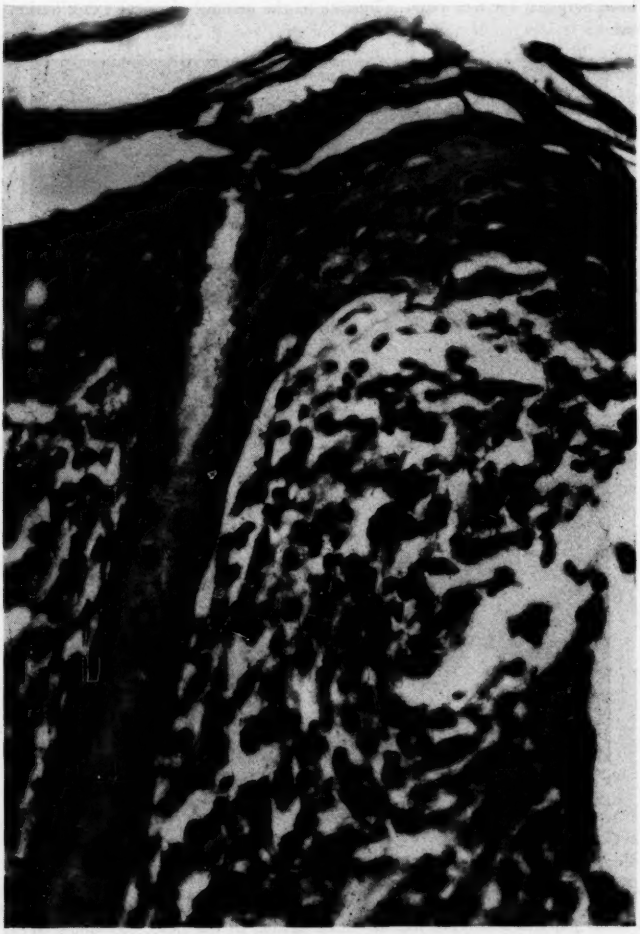


Fig. 2.—Characteristic histologic features of lichen nitidus present in one of the lesions on the face.

the duct of the sweat gland, the epidermis was thin and flat and there was no pigment within it. Just beneath the epidermis there were a few large chromatophores containing melanin pigment. About the opening of the sweat duct there was a small, sharply circumscribed mass of cellular infiltrate that filled the

papillary layer. This contained many epithelioid cells with a mixture of lymphocytes at the periphery. A narrow mantle of this dense cellular infiltrate extended more deeply about the sweat duct, but the sweat gland itself was not involved. The histologic diagnosis was lichen nitidus."

Department of Dermatology, Cook County Hospital.

CORRECTION

The correct address of the American Academy of Dermatology and Syphilology is P. O. Box 6565, Cleveland 1, and the annual meeting will be held December 2 to 7 in Chicago. Incorrect information is listed in the Directory of the July issue of the ARCHIVES, page 176.

Obituaries

CARL LANGLEY BRUNDAGE, M.D.

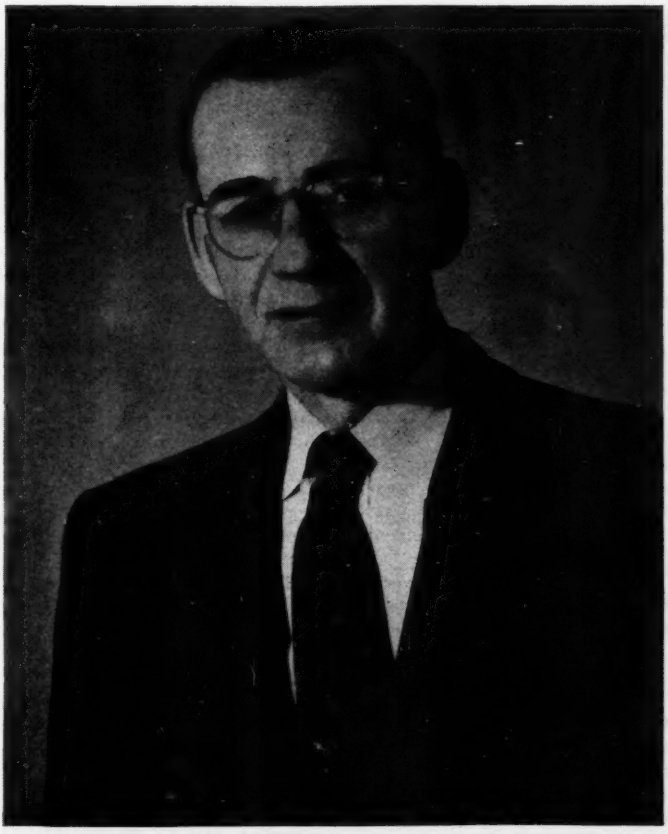
1895-1950

Dr. Carl Langley Brundage, Oklahoma City, was born in Scottsville, Kan., on Feb. 8, 1895. He received his elementary schooling in Thomas, Okla., and then entered the University of Oklahoma, where he earned a Bachelor of Science degree in 1918 and a doctor's degree in 1920. Dr. Brundage was a general practitioner in Thomas until the time he entered the University of Pennsylvania, where he received a Master of Science degree in dermatology in 1928. During this period of study he worked in the office of Dr. Jay F. Schamberg.

In 1928 he opened an office in Oklahoma City, where he practiced dermatology until his untimely death on June 2, 1950, from a cerebral hemorrhage. Dr. Brundage was clinical professor of Dermatology and Syphilology at the University of Oklahoma School of Medicine. He was a member of Phi Beta Pi fraternity, the American Medical Association, the American Academy of Dermatology and Syphilology, the Oklahoma Dermatological Society, the Oklahoma Academy of Medicine and the Oklahoma City Clinical Society.

Beloved by all his colleagues and patients, he will be remembered for his kindness and keen interest in the needs and problems of all who knew him.

A. Brooks Abshier, M.D.



CARL LANGLEY BRUNDAGE, M.D.
1895-1950

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

Samuel M. Peck, M.D., *Chairman*

Anthony C. Cipollaro, M.D., *Secretary*

Feb. 1, 1949

Erythema Induratum. Presented by DR. WILBERT SACHS.

M. S., a woman aged 29, born in Greece, was first seen by me on Jan. 11, 1949. Four months before, she had acquired a subcutaneous mass in the right buttock which soon grew larger and ulcerated through the skin. A bloody purulent drainage was noted, but there was no fever or tenderness. This process of ulceration and drainage has repeated itself four times since then. No treatment has been administered. The patient has lost 30 pounds (14 Kg.) during the past three years.

There is a firm, deep, subcutaneous, granulomatous mass, 2 inches (5 cm.) in diameter, involving the right buttock. The overlying skin is bound down and of a dark brown color. No ulceration is present at this time.

A blood count showed 11.6 Gm. of hemoglobin, 3,900,000 red blood cells and 4,400 white blood cells, with 60 polymorphonuclear leukocytes, 24 lymphocytes, 9 monocytes and 7 band forms. Urinalysis revealed no albumin or sugar. The tuberculin test elicited positive reactions to a dilution of 1 : 100,000. Roentgenograms of the chest and right hip revealed completely normal conditions.

Biopsy showed the epidermis to be essentially unchanged, with the basal cell margin intact. In the upper portion of the cutis there was a large number of dilated blood vessels, with very little cellular reaction. In the deep part of the cutis there were several tubercles and a moderate cellular reaction. The diagnosis was erythema induratum.

DISCUSSION

DR. S. IRGANG: Erythema induratum is a possibility, although the eruption is limited to the buttocks; however, one would expect to find lesions on the legs as well. Furthermore, I do not believe that a histologic diagnosis of erythema induratum is possible without examination of the subcutis. A foreign body granuloma should also be considered here, since the patient received intramuscular injections fifteen years prior to the appearance of the lesion.

DR. PAUL GROSS: It was my impression that this patient was ill. Some of the lesions are suggestive of tuberculosis of the hypoderm. In this case guinea pig inoculation and direct smears might demonstrate tubercle bacilli. Such observations would necessitate further search for visceral tuberculosis.

DR. E. T. BERNSTEIN: I think this is the first instance in which a diagnosis of erythema induratum of the buttocks has been suggested. It might be tuberculosis of the hypoderm, or it might be a foreign body granuloma. I suggest a diagnosis of tuberculosis of the hypoderm.

DR. WILBERT SACHS: The subcutis was examined, and there were very few giant cells and no necrosis, which observation would more or less rule out a foreign body granuloma and perhaps rule out tuberculosis of the hypoderm.

DR. S. IRGANG: I do not believe that a histologic diagnosis of erythema induratum is possible in the absence of caseous necrosis in the subcutis. The finding in the subcutis of epithelioid tubercles without necrosis should make one consider a diagnosis of Darier-Roussy sarcoid.

DR. WILBERT SACHS: It is not necessary to have necrosis to make a diagnosis of erythema induratum. Tubercles are observed in syphilis as in tuberculosis, but Satenstein said he was able to make a differential diagnosis between syphilis and tuberculosis, and I think I can make it, too. When there is a tremendous inflammatory reaction around the tubercles, and especially with some giant cells, Darier-Roussy sarcoid can be ruled out.

Vogt-Koyanagi Syndrome. Presented by DR. GEORGE M. LEWIS.

DISCUSSION

DR. BRUCE M. ESPLIN (by invitation): The Vogt-Koyanagi syndrome in its complete form is featured by uveitis, poliosis, vitiligo, alopecia and dysacousia. This patient demonstrates the syndrome as originally described in 1905 by Vogt, namely uveitis, poliosis and vitiligo. Alopecia and dysacousia were added to the entity in 1929 by Koyanagi. Nearly all the approximately 60 reported cases have been in the ophthalmologic literature. This situation is probably due to the fact that uveitis is invariably the presenting complaint and most serious component of the syndrome. One case was demonstrated before this group last year and subsequently reported. The ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY contained one report in 1948. The patient had a carcinoma of the breast but not of the thyroid. She had a toxic goiter.

Leiomyoma Cutis of the Arms, Back and Face. Presented by DR. WILBERT SACHS.

DISCUSSION

DR. BRUCE ESPLIN (by invitation): The patient gave a history of paroxysms of pain in these lesions, and they were found to be tender to palpation. The nodules were small, brownish to flesh colored, smooth and somewhat translucent and were distributed in small groups of two or three on the extensor surfaces of the arms, sides of the face and the back. Because of these features we suspected the diagnosis of leiomyoma cutis.

DR. SAMUEL M. KAUFMAN: The patient says that her mother has similar lesions on the neck. I wonder whether leiomyoma is familial.

DR. SAMUEL M. PECK: What was the clinical diagnosis?

DR. GEORGE M. LEWIS: Leiomyoma, made by one of the junior members of the staff.

DR. WILBERT SACHS: It is sometimes difficult to say whether a section is leiomyoma, neuroma or a combination of both, but in this particular lesion I was fortunate enough to find a pure leiomyoma without neural elements.

Lupus Vulgaris Treated Successfully with Calciferol Continually for Eleven Months. Presented by DR. ANTHONY C. CIPOLLARO.

Disseminated Sarcoid: Involvement of Skin Only. Presented by DR. GEORGE M. LEWIS.

Multiple Angiomas and Psoriasis. Kaposi's Sarcoma? Presented by DR. WILBERT SACHS.

A Case for Diagnosis (Angioblastoma?). Presented by DR. GEORGE M. LEWIS.

Dermatitis Herpetiformis Treated with Sulfapyridine. Presented by DR. MARGARET KLUMPP.

Mycosis Fungoides Treated with Antimony Potassium Tartrate. Presented by DR. GEORGE M. LEWIS.

Favus of the Scalp. Presented by Dr. Anthony C. Cipollaro.
Superficial Basal Cell Epithelioma. Presented by Dr. Wilbert Sachs.
Calcium Deposit (Secondary to Burn). Calcinosis Cutis (Localized). Presented by Dr. George M. Lewis.
Hypertrophic Lichen Planus. Lichen Planopilaris. Presented by Dr. George M. Lewis.
Epidermolysis Bullosa. Presented by Dr. Wilbert Sachs.
Recurrent Lichen Planus. Presented by Dr. Margaret Klumpp.
Granuloma Annulare. Presented by Dr. Margaret Klumpp.
Acne Varioliformis. Presented by Dr. Anthony C. Cipollaro.

CHICAGO DERMATOLOGICAL SOCIETY

Carl W. Laymon, M.D., *President*

James R. Webster, M.D., *Secretary*

April 20, 1949

A Case for Diagnosis. Presented by Dr. T. Cornbleet and (by invitation) Dr. D. Cohen and Dr. D. Musgrave.

R. S., a 40 year old Negro man, has had an eruption of the scalp and buttocks of one and one half years' duration. The first lesions were small nodules over the buttocks and scalp, which later discharged a foul-smelling yellowish material. At present, the scalp lesions have healed with scar formation and resultant alopecia. Numerous discharging sinuses remain in the inguinal and perianal regions.

On physical examination numerous areas of atrophy, scar formation and associated alopecia may be observed scattered over the scalp.

Over both buttocks are palm-sized indurated areas with scarring and atrophy. Numerous sinuses are found in this area and also in the inguinal region.

Laboratory examination gave the following results: urinalysis, normal; serologic picture, normal; hemoglobin, 70 per cent; red blood cell count, 3,200,000, and white blood cell count, 15,100, with 82 polymorphonuclear cells, 2 eosinophils, no basophils, 14 lymphocytes and 2 monocytes.

Culture of purulent material from sinus tracts was reported as growing "diphtheroids and Diplococcus pneumoniae."

Total protein was 7.4 Gm. per hundred cubic centimeters; the reaction to the Frei test was negative. Donovan bodies were not demonstrated. A biopsy was performed, and the report on it will be available at a later date.

DISCUSSION

Dr. Earle Pace: It seemed to me that the processes were essentially the same. On the buttocks and groins one would term the condition hidradenitis suppurativa. The involvement of the scalp is typical of perifolliculitis capitis abscedens et suffodiens. The face shows severe scarring, presumably from cystic acne of the conglobata type. All three disorders are perifollicular and form abscesses, low grade dissecting cellulitis, sinuses and irregular scars. I believe they are variants of the same process in a predisposed person.

Dr. Theodore Cornbleet: I cannot help but feel that these various lesions have a kind of sex linkage. The scalp lesions, which are comparable to perifolliculitis capitis abscedens et suffodiens, occur preponderantly and in my experience only in males, while the hidradenitis segment of the syndrome has a predilection for the female.

DR. S. J. ZAKON: I have seen similar cases in women. In the experience of my associates and me hidradenitis is much commoner in women, both white and Negro. We have also seen hidradenitis of the scalp with folliculitis and perifolliculitis in women.

I believe this patient requires massive surgical excision "saucerization" in order for any improvement to be produced. I do not think that with dermatologic therapy alone we can help this type of disorder.

DR. THEODORE CORNBLEET: Even though such scalp changes may be seen rarely in the female or the hidradenitis seldom in the male, it is my feeling that there is a kind of significant sex linkage. Acute disseminated lupus erythematosus may occur in the male, but it is thought of as occurring more commonly in the female. To me this thought is important, because it is from such a basis that we may proceed in our investigations and therapy with the hope of achieving success.

Lupus Vulgaris of Fifty Years' Duration, Successfully Treated with Ertron.® Presented by DR. JAMES H. MITCHELL and (by invitation) DR. J. W. GRAFFIN.

E. A., a white woman aged 56, acquired a lesion on her nose when she was about 8 years of age. Gradually, over the span of almost half a century, this eruption spread to her face, eyes and upper extremities, causing severe scarring and destruction. The previous use of numerous therapeutic agents was to no avail; these agents included starch given intradermally, roentgen and ultraviolet rays, vitamins and ointments. Although born in the United States, the patient lived almost the entire first six years of her life in Norway. In spite of the severe facial deformities and blindness, she has engaged in a relatively normal home life and has reared 7 of her children.

She has been followed in the eye clinic at Central Free Dispensary since 1940 because of severe scarring of the eyelids, conjunctivas and corneas in addition to bilateral cataracts and interstitial keratitis which have rendered her almost entirely blind.

In January 1947 treatment was started with a course of 150,000 units of ertron® (a concentrated vitamin D preparation) daily. After several months this had to be discontinued because of toxic symptoms. Ertron® was given again in November 1947, and treatment was continued, with several lapses, until January 1949. Since that time administration of ertron® has been discontinued because of a bout of virus pneumonia and erysipelas. There was a remarkable improvement in the lesions as illustrated by a kodachrome® picture taken in 1947, and at present there are only a few small active lesions. However, the blindness, scarring and deformities of the face remain unaltered.

Tuberculosis of the Skin (Lupus Vulgaris? Tuberculosis Verrucosa Cutis?) in an 8 Year Old Negro Boy. Presented by DR. I. M. FELSHER, DR. A. SLEPYAN and (by invitation) DR. W. ROSENBERG and DR. S. STEINBERG.

A Case for Diagnosis (Tuberculosis Cutis Verrucosa? [Unconfirmed Histologically]). Presented by DR. F. E. SENEAR and Staff.

DISCUSSION OF PRECEDING THREE CASES

DR. H. E. MICHELSON, Minneapolis: In Dr. Mitchell's case there evidently has been a pronounced improvement under the vitamin treatment. Therefore, it might be advisable to have a plastic surgeon see the patient now with the hope that surgical operation might improve the nostril.

In the case of the little Negro boy, I considered three types of tuberculosis: a primary external infection, tuberculosis verrucosa cutis and verrucous lupus vulgaris. I thought one could rule out the first because of the lack of adenitis, and I thought the picture in the microscopic section favored the diagnosis of lupus over verrucous tuberculosis. I think more information is needed about the patient, such as the results of the tuberculin test, state of the lungs and observations on the search for organisms.

DR. THEODORE CORNBLEET: I was quite impressed with the result achieved in Dr. Mitchell's patient. My associates and I had used ertron® for several years before we became acquainted with the experience of our European colleagues with calciferol. Our results with ertron® were mediocre compared with those obtained in this particular case. When we tried increasing the dose our patients became ill, and when the preparation was given in amounts that our patients tolerated we were not fortunate enough to see results comparable to those in Dr. Mitchell's patient.

DR. F. E. SENEAR: In spite of the fact that our patient gave a history of having had demonstrable tuberculosis we were very skeptical about the probability of the lesion of the hand being tuberculosis. The patient is engaged in an occupation during which he constantly has trauma to that part. He also gives a history of interfering with the lesion from time to time. Since the histopathologic picture did not support the diagnosis of tuberculosis we feel that the disorder is nonspecific.

Pemphigus of Hailey and Hailey (Recurrent Herpetiform Dermatitis Repens, Ayers and Anderson. Bullous Darier's Disease, Pels and Goodman. Dyskeratosis Bullosa Hereditaria, S. W. Becker and Obermayer). Presented by DR. H. RATTNER and DR. L. C. GREENFIELD (by invitation).

DISCUSSION

DR. HARRY R. FOERSTER, Milwaukee: The designation of benign pemphigus for the condition described by the Drs. Hailey is a confusing one to me. If this case is a typical one, I agree with those who prefer to call the condition a pemphigoid pyoderma. I recall 2 apparently identical cases. In each case the lesions appeared first on the back or side of the neck following trauma as an impetiginous, vesicular and bullous crusted eruption that extended in serpiginous fashion, proved resistant to treatment and recurred repeatedly after temporary healing. We considered the lesions of streptococcic origin, and they eventually responded to treatment along those lines. I believe the histologic section in the case seen today permits consideration of the diagnosis of a superficial streptococcus infection although there is much destruction and edema of the epidermis for a pyoderma and the infiltrate in the cutis is predominantly lymphocytic.

DR. GAROLD V. STRYKER, St. Louis: In my opinion the clinical condition of this patient fitted the diagnosis of benign familial pemphigus, though there was no familial history. Because of the histologic appearance, others have attempted to characterize this condition as an atypical type of Darier's disease, which, in turn, is thought to be the result of a vitamin A deficiency. In view of this contention, I inspected the eyes and found hyperkeratosis (Bitot spots) of the conjunctiva at the limbus on the lateral side of both eyes. These are rather pronounced for a young person. The Bitot spots are rather common in older people but usually occur in younger persons only when there is avitaminosis A.

Congenital Ectodermal Defect. Presented (by invitation) by DR. E. L. LAYDEN and DR. A. L. LORINCZ.

J. Y., a 13 month old female infant of Japanese descent, was seen at the University of Chicago Clinics on March 16, 1949, because of a congenital skin disorder.

She was born three weeks prematurely with epidermis apparently lacking over large portions of the back, scalp, arms and legs. Gradually a thin, red, hairless covering appeared over the denuded surfaces. This epidermis then thickened, but pigmentation has been irregular. Since the age of 3 weeks the infant has had an oozing, crusting, pustular dermatitis resistant to many types of therapy, involving the scalp and ears. The epidermis on the scalp has remained thin and the hair scanty.

All nails were absent at birth. These slowly appeared but in dystrophic form and at first on chronically pustular nail beds.

No teeth have erupted so far, and roentgenograms reveal absence of all the anterior maxillary teeth and of at least four of the anterior mandibular ones. The maxilla and nasal bones are small, and there is a bifid uvula. Observations on physical examination, except for the changes already mentioned, were essentially normal.

Sweat glands are present, as demonstrated by the starch-iodine technic, but are reduced to about one-third the number found in a normal control infant. Results in laboratory tests, including the Kahn serologic test, have been normal. The bone age and mental development are not retarded.

There is no known family history of a similar disorder.

Histologic examination of the scalp shows a thin epidermis with smoothed-out rete pegs. A bandlike infiltrate separated from the epidermis by normal connective tissue is present and consists of round cells and plasma cells. In the deeper part of the corium a horny cyst can be seen connected with a hair follicle. There are fewer follicles than expected on the scalp, and some of them seem to be atrophic. The blood vessels are dilated and show endothelial swelling.

DISCUSSION

DR. H. RATTNER: I saw the infant just a few hours after birth with the most striking cutaneous picture I had ever seen. Large areas of the body were denuded; there were denuded strips covering almost the entire back extending from the neck down to the buttocks. The limbs were stripped of skin, and there were denuded areas on the palms, though there were no blisters. The mother had not had a difficult labor, and delivery was without the use of instruments. There was no history of rubella during pregnancy. At the time I could think only of epidermolysis bullosa though I had never before seen a case that early.

DR. M. R. CARO: I agree with the diagnosis of congenital ectodermal defect, but I do not believe the scalp lesion as presented today is part of that picture. I believe the patches on the scalp are a combination of seborrheic dermatitis and folliculitis. I think they should be treated with some kind of mild ointment, like 1 per cent iodochlorohydroxyquinoline (vioform®) in petrolatum.

DR. E. L. LAYDEN (by invitation): I very much appreciate Dr. Caro's suggestion as to treatment of the scalp. Up to date we have had no success with different antiseptic ointments.

The history implies that there is a reduction in the number of sweat glands. Actually this will not be proved until we have compared this infant with a larger group of normal babies.

Hirsutism in a Patient with Arrhenoblastoma. Presented by DR. T. CORNBLEET and (by invitation) DR. D. COHEN and DR. S. BARSKY.

Secondary Syphilis: Patches in Seborrheic Areas. Presented by DR. D. OMENS and (by invitation) DR. H. OMENS and DR. S. BARSKY.

Kaposi's Varicelliform Eruption in a Girl with Atopic Eczema. Presented by DR. T. CORNBLEET and (by invitation) DR. H. SCHORR and DR. S. BARSKY.

Congenital Defect: Adenoma Sebaceum; Fibroma Durum; Subungual Hyperkeratosis. Presented by DR. H. RATTNER and (by invitation) DR. H. RODIN and DR. S. BARSKY.

Generalized Lichen Planus, Including Lesions on Scalp and Ears. Presented by DR. H. RATTNER and (by invitation) DR. H. RODIN and DR. D. MUSGRAVE.

Lichen Ruber Planus Verrucosus, More Pronounced on Leg with Varicose Veins. Presented by DR. MAURICE OPPENHEIM † and DR. WILLIAM YACULLO (by invitation).

Acute Leukemia (Lymphatic? Monocytic?). Acute Agranulocytosis? Presented by DR. T. CORNBLEET and (by invitation) DR. H. SCHORR and DR. D. MUSGRAVE.

A Case for Diagnosis (A Pigmentary Disturbance of Unknown Causation). Presented by DR. JAMES H. MITCHELL and (by invitation) DR. J. W. GRAFFIN.

Pemphigus Vulgaris: Herxheimer Reaction Following Roentgen Therapy to Liver and Spleen. Presented by DR. SAMUEL J. ZAKON and DR. AARON L. GOLDBERG (by invitation).

Solid Edema of the Lip. Presented by DR. F. E. SENEAR and Staff.

† Dr. Oppenheim died on Oct. 27, 1949.

Carl W. Laymon, M.D., *President*

James R. Webster, M.D., *Secretary*

May 18, 1949

Toxic Erythema With Wheal-Like Lesions Associated With Brill-Symmers Disease.

Presented by DR. T. CORNBLEET and (by invitation) DR. H. SCHORR and DR. S. BARSKY.

J. S. is a 21 year old white woman who first entered the Cook County Hospital in March 1949 with a three month history of chills, fever, weakness, anorexia, loss of weight, dizzy spells and cough.

On admission she presented an erythematous flush over both cheeks and the bridge of the nose. A generalized urticarial eruption lasting twenty-four hours was also present at that time. The patient has since had repeated transient episodes of facial erythema and generalized urticaria.

Biopsy of a lymph node soon after admission revealed giant follicular hyperplasia. The blood smears showed profound normocytic, normochromic anemia with a normal differential count. The bone marrow smear was abnormal but not diagnostic. Free acid was present in the stomach.

The liver and spleen are not palpable.

Adenopathy is minimal on gross examination.

The patient has made striking clinical improvement on treatment under an antipernicious-anemia regimen which included the administration of crude liver extract, 30 units intramuscularly twice weekly, and repeated blood transfusions.

Lymph node biopsy was reported by the Cook County Hospital pathology department as showing Brill-Symmers disease.

DISCUSSION

DR. S. M. BLUEFARB: The lymph nodes show the typical picture of the Brill-Symmers disease. There is an increase in the size and number of the lymph follicles. Clinically this girl is ill and toxic and there is pronounced secondary anemia. The bleeding tendency and erythema are part of a toxic process associated with the Brill-Symmers disease. The anemia and toxicity may be due to

some infectious process. If this infection can be found and corrected immediately I believe the process is reversible and the condition may show improvement. However, if the infectious element is not treated soon the prognosis does not appear to be good.

DR. THEODORE CORNBLEET: The eruptions on the skin change their appearance rapidly and disappear and reappear without warning. The lesions which the patient had only a few days ago and that I hoped to show you are now totally gone. Treatment with liver extract seemed to improve her condition noticeably, raising the question as to whether there could be an element of pernicious anemia present. There has not been an opportunity to see whether parallel blood changes accompany the rapidly shifting appearances of the eruption.

A Case for Diagnosis: Lichen Planus? Pemphigus? Presented by DR. M. EBERT and (by invitation) DR. V. LEAF and DR. S. BARSKY.

F. H. is a 79 year old Negro woman who has had a generalized skin eruption of three months' duration.

When the patient first visited our clinic two months ago she presented a generalized pityriasis-rosea-like pruritic eruption. The lesions have improved considerably since then. At present there is no pruritus.

The patient has always been in good general health.

She takes magnesia magma about once every two weeks for constipation.

Physical Examination.—Heart, lungs and mucous membranes are essentially normal. There is a symmetric eruption which is confined to the trunk and under surfaces of both arms. The eruption is densest in an area which extends 4 cm. to either side of the midline on the back. Individual lesions are annular and from 2 mm. to 1 cm. in diameter. Well developed lesions have threadlike palpable, raised borders with slightly hyperpigmented centers. On grattage, the border scales more than the center. There is no adenopathy.

Laboratory Examination.—The urine contained albumin; glucose and microscopic constituents were not present. The hemoglobin was 75 per cent; the red blood cell count, 4,100,000; the white blood cell count, 8,700; the serologic (Kahn) reaction, negative, and a roentgenogram of the chest, normal.

Histopathologic Picture (Lesion on Back).—There was moderate hyperkeratosis. There was no evidence of parakeratosis. There was pronounced atrophy with complete flattening out of the rete pegs. In places the epidermis was reduced to three or four rows of cells. The stratum granulosum was retained throughout. There was pronounced edema of the subpapillary layer. There was appreciable lymphocytic infiltration around two of the sweat ducts. A few lymphocytes were scattered throughout the edematous zone. In places the epidermis was separated from the corium, and in these areas there was liquefaction necrosis of the basal layer. The elastic tissue had almost completely disappeared from the edematous zone.

DISCUSSION

DR. CLARK W. FINNERUD: This case impressed me clinically as being an unusual manifestation of lichen planus. The threadlike border of the annular lesions which, according to the history, in some of the instances were bullous lesions in the beginning supports that impression. In spite of the fact that the microscopic section resembled lupus erythematosus more than it did lichen planus, I think this condition will prove to be lichen planus. In places in the section there is the sharp infiltrate that one would expect to see in lichen planus, but otherwise the section was not a very good example of lichen planus.

DR. MICHAEL H. EBERT: This case has been confusing clinically. The lesions today are not as they appeared two or three weeks ago. At that time I was quite impressed with the idea that the disease was lichen planus of the annular type in spite of the fact that there was no itching. After seeing the patient on repeated Mondays I changed my mind, even venturing the notion that the disorder was an atypical pityriasis rosea. I was rather surprised when the histologic diagnosis suggested lupus erythematosus. On a second look and particularly after a careful study of the section, I am inclined to believe the disease belongs to the pemphigus group. One could hardly call it pemphigus erythematosus since there are no lesions on the scalp suggesting lupus erythematosus. The lesions on the scapula fit into this picture. I must confess I have never seen a picture like this threadlike border of these discrete lesions.

The case is as difficult to interpret histologically as it is clinically. The pronounced atrophy may be due to age. There is no border of normal skin available for comparison. There is an extreme atrophy of the epidermis which might be due to the patient's age. In favor of lichen planus there is proliferation of the granular layer. The granular layer makes up most of the epidermis. Separation of the epidermis from the corium is sometimes present in lichen planus. The character of the infiltrate and the distribution of the infiltrate are not those of lichen planus. My diagnosis is pemphigus, possibly a bullous pemphigus erythematosus.

Pityriasis Lichenoides Chronica of Juliusberg (?). Presented by DR. J. H. MITCHELL and (by invitation) DR. J. W. GRAFFIN.

J. O., a woman aged 20 years, about five years ago acquired a generalized papular eruption. This eruption has undergone moderate remissions and exacerbations but has had only one complete remission for a two week period. These lesions are not associated with pruritus, and the patient's general health has been excellent.

This well nourished woman presents a generalized papular eruption which spares the face, palms and soles and mucous membranes. The papules are numerous, discrete and reddish. There is a thin white scale covering many of the papules, but this does not powder on grattage.

The Kahn test of the blood gave negative reactions. A histologic section is presented from a typical papule on the arm.

Parapsoriasis. Presented by DR. F. E. SENEAR and Staff.

A Case for Diagnosis: Lymphoblastoma? Presented by DR. F. E. SENEAR and Staff.

A Case for Diagnosis: Parapsoriasis en Plaque? Presented by DR. F. V. HAUSER (by invitation) and DR. E. L. LADEN (by invitation).

DISCUSSION OF PRECEDING FOUR CASES

DR. M. H. EBERT: The case that I was particularly interested in was the one presented by Dr. Mitchell as the Juliusberg type of pityriasis lichenoides chronica. I was interested because I was able to demonstrate a sign that I read in Brocq's book on dermatology published in 1899. If you scrape off the scales you will see many small punctate hemorrhages. This sign was beautifully illustrated in this case.

DR. S. W. BECKER: In addition to the generalized eruption, the girl presented by Dr. Mitchell presented linear leukoderma on the left arm. This stripe has been hypopigmented all her life, but no one else in the family has a similar disorder. It is obviously partial albinism.

DR. F. J. SZYMANSKI (by invitation): In the case of the man shown by Dr. Senear examination of the histologic section shows an infiltrate high in the corium. The number of cells in the infiltrate is not very large, but some of the cells showed pyknosis and karyorrhexis. In addition, there are groups of cells invading the epidermis. Histologically we can consider this case compatible with a diagnosis of the premycotic stage of mycosis fungoides.

DR. MARCUS R. CARO: About five years ago I saw Dr. Mitchell's patient once. At that time her eruption was exactly the same as it is today and I made the diagnosis of pityriasis lichenoides chronica.

DR. F. E. SENEAR: With regard to the Negro girl with pityriasis lichenoides chronica, she showed a sign in that disease, which the French pointed out, better than I have ever seen it before. That was the powdering of the skin on grattage.

With regard to the man, I do not think we had considered the possibility of a mycotic infection. We thought he might have a premycotic stage of mycosis fungoides. The thing that inclined me toward that as a diagnosis was that some of these lesions were distinctly retiform, as we see them frequently in the early stages of mycosis fungoides, a point which I thought more in favor of that disease than parapsoriasis. We observed that as the lesion extended peripherally it was with an infiltrating margin, so that the activity at the edges was much greater than in the center of the patches, while in lesions of parapsoriasis there is a uniform infiltrate. The observation has been made frequently that cases of supposed parapsoriasis of the en plaque type terminate as mycosis fungoides. The advanced age of the man will speak for the possibility of mycosis fungoides more than the other. Unfortunately we were not able to obtain a blood count on this patient in time for presentation today. He was seen only a few days ago. At this time I apologize also for the incompleteness of the presentation of the other patient. He entered the hospital only the day before yesterday, and we have had no opportunity to study him.

Psoriasis Vulgaris Universalis Treated with Undecylenic Acid (Declid®). Presented by MAURICE OPPENHEIM† and DR. WILLIAM A. YACULLO.

D. G., a white man aged 28, consulted us on May 9, 1949. He stated that a general practitioner directed the administration of undecylenic acid (declid®) in the following manner: The first week he took 6 capsules a day, each 0.44 Gm.; he gradually increased the dosage until he took 20 capsules daily for four weeks from April 1 until May 9.

We advised him to discontinue the medication because at this time he presented an erythroderma psoriaticum. His pruritus became worse during undecylenic acid treatment. He complained of loss of appetite, diarrhea and a loss of 20 pounds (9 Kg.).

The amount of medication was 500 capsules, each 0.44 (Gm.), for a total of 200 Gm.• We had seen this patient on account of his psoriasis in 1944.

† Dr. Oppenheim died on Oct. 27, 1949.

A Case for Diagnosis: Scleroderma with Bullous Lesions? Presented by DR. F. E. SENEAR and Staff.

DISCUSSION

DR. FREDERICK R. SCHMIDT: I should consider porphyria.

DR. MICHAEL H. EBERT: I believe this eruption started as a bullous eruption followed by the hyperpigmentation and sclerodermatous change of face, neck and other parts of the body. I think it could be an unusual type of scleroderma because

all those changes—bullous eruption, abnormal pigmentation and hyperpigmentation, in addition to depigmentation—can be seen in scleroderma.

DR. FRANCIS E. SENEAR: We consider both things mentioned, cutaneous porphyria and scleroderma. I have never seen anything approaching the degree of destruction that occurs here in connection with sensitivity to light. As Dr. Ebert pointed out, there is much sclerodermatous change here. Some of the lesions look very much like those that we see in dermatitis factitia. I saw the patient about one week ago, and he had a number of lesions that were covered with a dense adherent crust, much as are those lesions produced by some caustic agent. Dr. Oliver saw him and felt the same way. Clinically the lesions had that appearance. We have the reports on the biopsies performed in Milwaukee. According to the patient's statements—and, by the way, he speaks very intelligently—those who examined him there were unable to make any histopathologic diagnosis though he was under dermatologic care.

The question of porphyria was not investigated there. We questioned him about red urine. He insisted that he did have it at times, whatever that may mean.

A Case for Diagnosis: Lichen Planus? Presented by DR. EDWARD A. OLIVER and Staff.

C. R., a 28 year old white woman, was first seen in the Dermatology Clinic, Northwestern University Medical School, on May 11, 1949, with the complaint of an eruption on the legs.

The patient stated that about five and one-half years ago an eruption had appeared in the region of the left ankle and had disappeared spontaneously in a few months. About two and one-half years ago the eruption recurred as small patches about both ankles and gradually spread to the legs and feet. There have been no remissions since the time of recurrence, and no individual lesion has involuted although the erythema has been observed to vary somewhat in intensity from day to day. Itching, of moderate severity, has been present day and night, is aggravated by nervous stress and is partially relieved by scratching.

The patient's general health has been good; she has no complaints other than her skin condition: however, she has gained about 40 pounds (18 Kg.) in the past six months. Roentgenograms of the chest in November 1948 and in February 1949 revealed no abnormalities.

Examination reveals closely set papules and nodules 1 to 10 mm. in diameter on the dorsa and sides of the feet, on the distal half of the legs and in palm-sized areas just distal to both patellas. Individual lesions are irregularly shaped, slightly elevated and flat topped to convex; some are smooth and shiny, while others exhibit a fine silvery scale. New lesions are dusky red; older ones have a violaceous tinge. Occasional flat flaccid bullae 4 to 8 mm. in size with limpid contents are seen. On palpation the lesions are soft, and the color fades completely on compression.

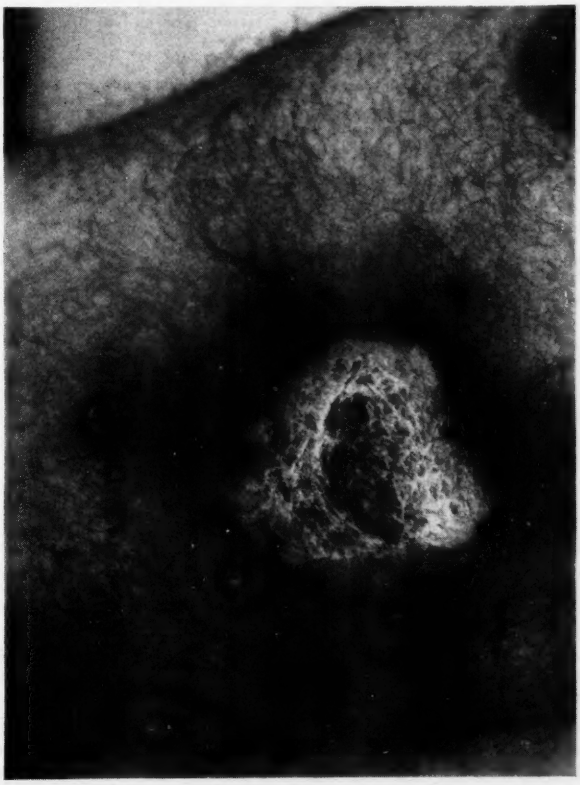
Past treatment has included the application of ointments, wearing of elastic stockings, administration of bismuth and mercury preparations by injection and roentgen ray therapy, none of which has caused involution of the lesions. Congo red injected locally previously revealed no amyloid.

Results of laboratory examinations were as follows: red blood cell count, 4,860,000; hemoglobin, 15.5 per cent, and white blood cell count, 7,650, with a differential count of 56 polymorphonuclear cells, 2 eosinophils, 4 basophils, 33 lymphocytes and 5 monocytes. Results of urinalysis were within normal limits. The Wassermann and Kahn reactions were negative. The basal metabolic rate has not been determined.

Biopsy specimens are presented.

DISCUSSION

DR. CARL W. LAYMON, Minneapolis: In the early 1900's Radcliffe Crocker described a case of lichen planus in which a noteworthy feature was that the lesions could be obliterated by pressure. In addition, there was telangiectasia on the face. He called it lichen planus erythematosus. In 1926, Dr. Charles Freeman of St. Paul reviewed the literature and reported a case. I saw his case, which closely resembled this one. The woman today had a few



Scaly patch of morphea (case presented by Dr. E. M. Smith Jr. for Dr. A. W. Stillians).

telangiectatic vessels, but not many. I think this is the same type of case which Crocker described.

DR. MICHAEL H. EBERT: Dr. Spinka gave me an opportunity to see this case some time ago, and we were impressed with the idea that it was a variant of lichen planus. However, the histopathologic picture does not fit with lichen planus or anything else.

DR. MARCUS R. CARO: Sections from this case were presented at the Dermatopathology Round Table at the Academy meeting last December. After considerable study and discussion it was agreed that no histopathologic diagnosis could be made.

DR. CARL W. LAYMON: There were quite a few sections, some of which were nondiagnostic. There were two sections in which there was a marginated infiltrate in the upper part of the cutis. There is some question as to whether there is such an entity as lichen planus erythematosus.

DR. EDWARD A. OLIVER: When we first examined these lesions they looked papular and shotty, but now they are soft. The suggestion of lichen planus is the most likely one we have. We considered lichen planus bullosus, but the pathologist gave us no help.

Nevus Unius Lateris Involving the Neck of an Infant. Presented by DR. D. OMENS and (by invitation) DR. H. OMENS and DR. D. MUSGRAVE.

A Case for Diagnosis: Granuloma (Annulare?). Presented by DR. T. CORNBLEET and (by invitation) DR. D. COHEN and DR. S. BARSKY.

Carcinoma Cutis of Right Breast, Back, Scalp and Left Axilla: Primary Source Unknown. Presented by DR. D. OMENS and (by invitation) DR. H. OMENS and DR. S. BARSKY.

Huge Basosquamous Cell Epithelioma of the Face. Presented by DR. D. OMENS and (by invitation) DR. H. OMENS and DR. D. MUSGRAVE.

Disseminated Morphea. Presented by DR. T. CORNBLEET and (by invitation) DR. D. COHEN and DR. D. MUSGRAVE.

Scaly Patch of Morphea. Presented by DR. E. M. SMITH JR. for DR. A. W. STILLIANS.

Pemphigus Vegetans with Dermatitis Medicamentosa. Presented by DR. C. W. FINNERUD, DR. F. J. SZYMANSKI (by invitation) and DR. J. M. RIDDELL (by invitation).

A Case for Diagnosis: Tinea of Nails and Skin? Presented by DR. MICHAEL H. EBERT and (by invitation) DR. ALLEN S. PEARL JR.

Von Recklinghausen's Neurofibromatosis. Presented by DR. LOUIS RUBIN (by invitation).

A Case for Diagnosis: Ulcer on Cheek. Presented by DR. E. M. SMITH JR.

Urticaria Pigmentosa, Mixed Maculonodular Type, in a 7 Month Old Infant. Presented by DR. JULIUS GINSBERG and (by invitation) DR. SIDNEY J. KAPLAN.

LOS ANGELES DERMATOLOGICAL SOCIETY

Maxwell Wolff, M.D., *Chairman*

Jud R. Scholtz, M.D., *Secretary*

May 10, 1949

Lipomelanotic Reticuloendotheliosis of Pautrier. Presented from the Dermatology Service, Los Angeles County Hospital.

C. H., a 24 year old American Negro, first noticed a moist eruption in the popliteal areas in January 1948. After extensive and vigorous local self medication, he was admitted to the dermatology ward the following September, at which time he presented a dry, itching eruption involving the dorsal surfaces of the hands and feet, the forearms, genitalia and popliteal areas. There was also pronounced generalized lymphadenopathy.

A few weeks after admission the dermatitis became universal and exfoliative, the scalp and body hair began falling, and there was a decided increase in the lymphadenopathy. By February 1949 there was total alopecia except for the eyelashes, the color of the skin had changed from that of a dark Negro to that of a blond and gynecomastia had developed.

On March 3, 1949, the daily administration of BAL (2, 3-dimercaptopropanol) by intramuscular injection was begun, and since that time improvement has been slow but steady. A growth of fine white hair has appeared on the scalp, face, inguinal and axillary areas. Before the use of BAL, penicillin, crude liver given by intramuscular injection, antihistamine drugs, vitamin A, the B complex, ascorbic acid, neostigmine (prostigmin®) and sodium thiosulfate were used.

Physical examination reveals a young man of light complexion but with the facial features of a Negro. There is fine short white hair on the scalp, face and axillary and pubic areas. There is pronounced generalized lymphadenopathy. There

is evidence of universal involvement of the skin, some areas showing only a residual erythema and scaling and other areas showing lichenification. The feet are swollen, and there is some maceration of the skin between the toes.

Laboratory studies revealed an abnormally low amount of serum albumin on two determinations, a 40 per cent eosinophil count with only a slight increase in the total white cell count in the peripheral blood, eosinophilia without evidence of lymphoblastoma in the examination of the sternal marrow, negative reactions to agglutination tests for typhoid, paratyphoid, typhus, Brucella and Pasteurella tularensis infections. Results ot stool examination for parasites were negative. Roentgenologic examination of the chest revealed no adenopathy.

DISCUSSION

DR. ARNE INGELS, San Francisco: I subscribe to the diagnosis and compliment the working-up of the case. I also think that there are many features of psoriasis in this case, a forerunner of reticuloendotheliosis, perhaps, and a discrepancy between the observations on histopathologic examinations and the clinical picture. I was struck first of all by the lichenification and tumefaction in all areas and the depigmentation. However, the thickened nails, which may be a part of this disorder, and plaques of the flexor surfaces and palms and soles may also be seen as features of psoriasis. In my examinations, I have been fortunate to see histopathologic features of psoriasis in many cases which otherwise would be deemed straight reticuloendotheliosis. In my opinion, many cases may be more or less latent psoriasis to start with. There was also a thickening of the palms and soles so easily explained on the basis of the present diagnosis with nail changes. The involvement of the extensor surfaces and the arthritis complained of need more explaining. The patient stated definitely that he has sore joints, not only when walking but also when at rest. The sections were of the kind in which the general pathologist will overlook the psoriatic features also present. The skin definitely showed psoriatic structure—namely acanthosis, colliquative degeneration, microabscesses, club-shaped papillary bodies and dichotomic branching—enough for a diagnosis of an underlying psoriasis. After seeing the lymph glands hastily I want to consider lymphoblastoma.

DR. HAROLD C. FISHMAN (by invitation): I think this is a pretty typical example of lipomelanotic reticulosis, described in 1937 by Pautrier and Woringer. They described 11 cases of chronic dermatoses associated with generalized lymphadenopathy of special histologic features. This is the first case associated with depigmentation that I have ever seen, the other 3 cases that I am familiar with showing pronounced melanotic pigmention. Usually the dermatosis, both clinically and histologically, is not very clearcut or typical of any definite disease. It may resemble any lichenified or eczematous eruption. However, the lymph nodes have a very characteristic, constant histologic picture. There is disorganization of the normal architecture, reticulum cell hyperplasia, melanin and lipid deposition and frequently many eosinophils. The picture here, I think, is both clinically and histologically as good a one as can be found. The importance of its recognition is in differentiation from lymphoblastoma, such as Hodgkin's disease.

DR. SAMUEL AYRES JR.: There is something about this case that is strongly reminiscent of an arsenical reaction. The patient was treated with arsenicals for syphilis prior to the onset of his dermatosis. He said that there was some lapse of time between the last injection and the onset of his skin trouble, but I don't think that this rules out the possibility of such a connection. Arsenic can produce a total alopecia as well as erythroderma. It can also cause nail changes. Since the use of BAL therapy, the whole process has been in reverse, which observation would support the likelihood of the condition's being of arsenical origin.

DR. ERNEST FOX: Two years ago at a meeting of the Los Angeles Dermatological Society, Dr. Obermayer and I presented a case of lipomelanotic reticulosis in a patient with lichen planus. The microscopic observations in the sections from that patient were similar to those which we have just seen for the patient now being discussed. I wish to point out and emphasize that any chronic pruritic dermatitis may result in lipomelanotic reticular hyperplasia of the lymph nodes. The latter is a benign manifestation secondary to the primary pruritic dermatitis; the trauma created by scratching results in increased formation of melanin and increased liberation and mobilization of both melanin and fat particles, which enter the cutaneous lymphatic vessels and are phagocytosed by the reticular cells; the amounts of pigmentation and fat are dependent, therefore, on the duration and severity of the pruritus and scratching. As examples of other pruritic dermatoses in which the lymph node changes characteristic of lipomelanotic reticular hyperplasia may be found I mention, first, 3 cases of exudative chronic discoid and lichenoid dermatosis (Sulzberger and Garbe) reported by Emery Koesard and, second, monocytic leukosis of long duration accompanied with considerable pruritus. In the latter disease, cellular alterations in keeping with the leukemia will be present in addition to those of lipomelanotic reticular hyperplasia.

Hidradenitis Suppurativa of the Axillas, Neck and Groins. Presented from the Dermatology Service, Los Angeles County Hospital.

DISCUSSION

DR. H. J. TEMPLETON, Oakland, Calif.: I agree with the presenter's diagnosis. I used to think this disease occurred only in the axilla, but it does occur in and about the apocrine glands on the buttocks. I suppose, in differential diagnosis, one would have to consider amebic abscesses and the deep mycoses, and I wonder how closely this disorder is related to dissecting cellulitis of the scalp. As to therapy, I would suggest a trial of streptomycin or aureomycin, combined with more radical removal of the undermined skin with the cautery. I would leave the lesion open and let it granulate in.

DR. WALTER R. NICKEL, San Diego, Calif.: I feel that the treatment is surgical removal.

DR. M. E. OBERMAYER: We have all seen patients with hidradenitis in whom the involvement of the apocrine glands is so extensive and the response to treatment so refractory as to constitute a serious problem. I know of a man in this city who has been completely incapacitated because of this disease for more than three years. Dr. Templeton is correct in advocating the use of the newer antibiotic agents, and I have seen good symptomatic results from the use of aureomycin after pencillin therapy had failed. I believe, however, that a more logical therapeutic approach would be an attempt to change the hormonal imbalance which, as in acne conglobata, may be the underlying cause of the disease. I would suggest the administration of massive doses of estrogenic compounds, perhaps in the form of implantation, as was advocated by Barber of London.

DR. SAMUEL AYRES JR.: I was not aware of the fact that apocrine glands were on the neck also. Typical acne lesions can occur on the buttocks as well as on the face, and acne conglobata can also occur in the same areas. At any rate, I think the process is similar, whether sebaceous or sweat glands are involved. I often wondered whether there was some spreading factor which the bacteria liberate which might account for this type of lesion. It is not just an infection, but it seems there must be something the bacteria do which changes the tissues

themselves. At present we have under our care a patient with similar lesions on the face and neck who has preauricular sinuses. It occurred to me that in some of these cases there might be congenitally defective sebaceous glands.

CLEVELAND DERMATOLOGICAL SOCIETY

Earl W. Netherton, M.D., *President*

George H. Curtis, M.D., *Secretary*

Gerard A. DeOreo, M.D., *Reporter*

May 19, 1949

Sarcoidosis: Involvement of Scalp. Presented by DR. H. A. HAYNES JR. and DR. J. H. STRAUCH.

Miss M. R., a white woman aged 56, presents the complaint of a gradually spreading eruption on the scalp present for ten years, beginning on the frontal area and progressing toward the vertex. The eruption is associated with partial to complete loss of hair in the involved areas and with some adherent scales.

The patient is a native-born American. She has had no contact with tuberculosis.

The frontal area and vertex of the scalp present a diffuse atrophy, with partial alopecia. The border of the lesion presents numerous yellow-brown pea-sized macular lesions, which have an apple jelly color on diascopy. Slight infiltration of the border is present, but there is no ulceration. Two reddish brown pea-sized papules are also present on the bridge of the nose.

The reaction to first strength precipitated protein derivative was slightly positive. Results of serologic examination were negative. Roentgenologic examination of the fingers showed slight osteoporosis. A roentgenogram of the chest revealed mild cardiac enlargement and probable sarcoidosis of the lymph nodes of both hili. Histologic examination of the scalp biopsy showed typical collections of epithelioid cells in the corium. There was no plasma cell infiltration or giant cell formation as seen in tuberculosis. The results of inoculation of tissue into guinea pigs were negative. There was reversal of the plasma albumin-globulin ratio.

No therapy has been given since October 1948. Previously, calciferol therapy for over two months produced little change. In the past five months there has been some regression of the disease, with regrowth of some hair on the vertex. Glass-pinhead-sized yellowish nodules are still present, and these areas become covered with a yellowish white adherent scale.

Prurigo Ferox (Prurigo Gravis; Prurigo of Hebra). Presented by DR. H. A. HAYNES JR. and DR. J. H. STRAUCH.

Mrs. M. G., aged 59, presents the complaint of an intensely pruritic eruption on the legs and arms of thirty-nine years' duration. The pruritus comes in crises, which are uncontrollable. The crises subside only after excoriation of almost every nodule. Friction on a single nodule starts pruritus of all the lesions. The eruption has not interfered with adequate nutrition.

The patient has never been entirely free of lesions since the age of 20. The eruption gradually progressed to involve both legs. Two years ago eight roentgen ray treatments to the lower part of the legs were given, with little change.

The patient is a well nourished, anxious, somewhat depressed, pale middle-aged woman. She presents excoriated nodular lesions covered with sanguineous crusts on the thighs, knees, legs and ankles, varying from 0.5 to 1.5 cm. in diameter. Most lesions are discrete, with some tendency to confluence on the anterior aspect of the legs. Scattered excoriated nodules are present on the wrists. The eruption stops sharply on the upper parts of the thighs, with no lesions above the inguinal folds. Mucous membranes appear normal. Femoral lymph nodes are moderately enlarged.

Histologic examination of the lesion on the knee showed "well marked hyperkeratosis of the epidermis, moderate acanthosis and a definite increase in the granular layer. There was only slight liquefaction in the basal layer of the epidermis. An inflammatory infiltrate consisting chiefly of lymphocytes was of only moderate extent and was confined to the superficial portion of the corium. There was slight fibroblastic proliferation superficially in the corium. No evidence of amyloidosis was present. A localized purulent infiltrate was present on the surface in the region where the epidermis was thinned."

The patient received a total of twenty-seven weekly injections of bismuth arsphenamine sulfonate (bismarsen®), 0.1 Gm. intramuscularly, and was given ½ grain (30 mg.) of phenobarbital three times a day. Twelve roentgen ray treatments of 75 r each were given to the knees and lower parts of the thighs. The pruritus was unrelieved, and the patient continued to excoriate the lesions. Occlusive dressings to the lower legs, with 5 per cent ichthammol (ichthyol®) paste and an elastoplast® bandage, were applied weekly. After nine weeks the leg lesions were flat and apruritic. The patient continued to excoriate the thigh lesions and was unable to tolerate dressings on the thighs for more than five days, tearing the bandages off in crises of pruritus. The oral administration of sulfapyridine and diphenhydramine (benadryl®) produced no change in the lesions or symptoms. Repeatedly the lesions were seen with a vesicle with hemorrhagic contents on top of each nodule. The application of phenindamine (thephorin®) ointment produced no relief. Freezing of the nodules with solid carbon dioxide resulted in their partial destruction and relief of pruritus. On Nov. 9, 1948, and on March 8, 1949, numerous flaccid bullae were present on both legs; these disappeared after the use of occlusive dressings for two weeks.

Pseudoxanthoma Elasticum Hidradenitis. Presented by DR. H. A. HAYNES JR. and DR. J. H. STRAUCH.

Mrs. J. L., aged 45, states that since early childhood she has known certain areas of her skin to be abnormal, with no great change through the years. During the past two years she has had recurring tender red nodules in the axillas, with foul-smelling moist drainage.

The patient, 1 of 8 siblings, states that her father's and mother's skin was entirely normal and that she knows of no further family background of a similar condition. Of the 8 siblings, 1 sister has the same condition in the axillas, present since childhood, and 1 brother has similar changes at the sides of the neck.

Examination reveals an extensive abnormality at the sides of the base of the neck, in and extending beyond both axillas, on the flexor surfaces of the wrists, on the lower part of the abdomen, the pubic region and the crural folds and extending down the medial aspects of the thighs to the knees. These changes consist of a dry, leathery looseness of the skin, with decreased elasticity. The surface of the skin resembles Scotch grain leather, with numerous closely aggregated yellow, pinhead–sized papules. In addition, both axillas present pea-sized to cherry-sized red, indurated nodules, tender to pressure, many of which have central sinuses with foul-smelling sebaceous and seropurulent drainage.

The patient has refused permission for biopsy and for surgical excision and subsequent plastic repair of the infected areas.

Filtered roentgen ray therapy, intramuscular administration of penicillin and local medication applied to the axillas have resulted in no improvement.

ADDITIONAL NOTE.—The aforementioned sister, aged 31, is also presented with the same, but milder, changes involving the axillas and cubital fossae.

DISCUSSION

DR. H. A. HAYNES JR.: This is a most extensive dermatosis, involving over 50 per cent of the skin surface. We have been trying to persuade the patient to have plastic surgical repair of the axillas. Does anyone know of postoperative complications that might occur by virtue of the pseudoxanthomatous change?

A Case for Diagnosis: Erythema Elevatum Diutinum? Rheumatic Nodules? Presented by DR. A. L. LEIBY.

Granuloma Annulare. Presented by DR. A. L. LEIBY.

Telangiectasia of Pregnancy. Presented by DR. H. A. HAYNES JR. and DR. J. H. STRAUCH.

Aphthous Ulcers of Mouth and Genitalia (Ulcus Vulvus Acutus; Periadenitis Mucosa Necrotica Recurrens). Presented by DR. A. L. LEIBY.

Parapsoriasis en Plaque. Presented by DR. M. J. GIBANS.

Mycosis Fungoides. Presented by DR. FRANK M. MCDONALD, Akron, Ohio.

A Case for Diagnosis: Lupus Erythematosus? Presented by DR. H. A. HAYNES JR., and DR. J. H. STRAUCH.

Sebaceous Adenomatoid Hyperplasia; Chromatophores (Significance Undetermined). Presented by DR. M. J. GIBANS.

Urticaria Pigmentosa. Presented by DR. M. J. GIBANS.

BROOKLYN DERMATOLOGICAL SOCIETY

E. Almore Gauvain, M.D., *President*

Samuel I. Greenberg, M.D., *Secretary*

May 16, 1949

Erythema Multiforme Bullosum (Due to Sulfonamides). Presented by DR. A. J. GEWIRTZ.

Nevus Unius Lateris. Presented by DR. B. BENDER.

Pustular Bacterid of Palms and Soles. Presented by DR. M. J. CANTOR.

Nummular Eczema. Presented by DR. E. ALMORE GAUVAIN.

A Case for Diagnosis: Drug Eruption (Phenolphthalein?)? Presented by DR. MAX LERNER.

A Case for Diagnosis: Melanosis of Riehl? Presented by DR. SAMUEL I. GREENBERG.

Keratosis Palmaris et Plantaris. Presented by DR. A. J. GEWIRTZ.

E. Almore Gauvain, M.D., *President*

Samuel I. Greenberg, M.D., *Secretary*

Oct. 17, 1949

A Case for Diagnosis: Lymphangioma Circumscripta? Presented by DR. IRVING N. HOLTZMAN.

Mycosis Fungoides. Presented by DR. LOUIS CHARGIN.

Alopecia Areata, Becoming Almost Total. Presented by DR. LOUIS CHARGIN.

Thrombopenic Purpura and Pruritus Due to Benzol Poisoning. Presented by DR. M. J. CANTOR.

Acrodermatitis Continua (Hallopeau). Presented by DR. M. J. CANTOR.

Scleroderma, Circumscribed. Presented by DR. I. N. HOLTZMAN.

Chronic Exudative Discoid and Lichenoid Dermatosis (Sulzberger and Garbe). Presented by DR. SAMUEL I. GREENBERG.

I. N. Holtzman, M.D., *President*

Samuel I. Greenberg, M.D., *Secretary*

Nov. 21, 1949

Cutis Hyperelastica (Ehlers-Danlos Syndrome). Presented by DR. JACOB SKEER.
A Case for Diagnosis: Pityriasis Rubra Pilaris? Presented by DR. LAWRENCE FRANK.
Parapsoriasis. Presented by DR. IRVING N. HOLTZMAN.
A Case for Diagnosis: Lichen Planus? Psoriasis? Arsenical Dermatitis? Presented by DR. ROBERT L. REIN.

MINNESOTA DERMATOLOGIC SOCIETY

Robert R. Kierland, M.D., *President*

Elmer T. Ceder, M.D., *Secretary*

Sept. 11, 1949

All patients were presented by Dr. Paul A. O'Leary, Dr. Hamilton Montgomery, Dr. Louis A. Brunsting and Dr. Robert R. Kierland.

Chronic Porphyria with Cutaneous Manifestations.

R. H., a 23 year old farmer, was presented before the Society three years ago, with a condition suggestive of porphyria. The diagnosis has been confirmed. He has had the unusual combination of symptoms of acute and chronic porphyria, and his record has been described in full (Brunsting, L. A., and Mason, H. L.: Porphyria with Cutaneous Manifestations, ARCH. DERM. & SYPH. **60:** 66 [July] 1949).

In the past two years, since his recovery from the acute phase of the disease, the patient has been observed periodically while carrying out his regular work as a farmer. He is in good physical condition. The skin of the exposed surfaces of the face and neck shows a slight pigmentation, and there is a reddish blue suffusion. On the dorsa of the hands there are scars of healed blisters and a few crusts as a reaction from slight trauma. The skin about the nose, cheeks and forehead is slightly thickened and roughened.

Recent tests of liver function showed only slight retention of the sulfobromophthalein sodium dye. The urine, although normal in color, has consistently shown large amounts of porphyrins. On Aug. 17, 1949, the report was as follows: 562 micrograms of uroporphyrin, 7.9 units of porphobilinogen and 1,090 micrograms of coproporphyrin per twenty-four hours.

Chronic Porphyria with Cutaneous Manifestations.

L. C., a 46 year old butcher and farmer, for the first time, early this summer, noted blisters on the dorsa of the hands which formed at the sites of minor trauma, particularly after exposure to sunlight. There were no systemic complaints, no record of discolored urine and no history of abdominal colic or urologic disturbances in the past, for the patient or the members of his family.

Examination revealed a peculiar bluish red suffusion of the exposed skin of the face and neck and on the dorsa of the hands and fingers. The skin was pigmented, and in several areas there were small blisters, unruptured and ruptured,

some with secondary infection and ecthyma and a few healed with scarring. There was a history of obesity and chronic alcoholism extending over a period of more than twenty years.

Examination revealed the weight of the patient to be 154 pounds (70 Kg.). There were no gross disturbances observed in the physical examination. Spectroscopic examination of the blood revealed normal conditions: cell volume measured 50 per cent, and hemoglobin was 14.6 Gm. per hundred cubic centimeters. The urine was a little darker than normal but not of port wine hue. Fluoroscopic examination of the acidified urine revealed primary fluorescence.

On Aug. 2, 1949, the examination of a twenty-four hour specimen of urine revealed 6,570 micrograms of uroporphyrin and 1,270 micrograms of coproporphyrin. The test for porphobilinogen gave negative rsults. There was a slight retention of the dye in the blood test for liver function.

In the treatment alcohol was interdicted and a dietary program was instituted as in hepatic cirrhosis.

DISCUSSION OF CASES OF PORPHYRIA

DR. R. NOMLAND, Iowa City (by invitation): My associates and I have not found porphyria in several cases of dermatitis from sunlight or in prurigo or urticaria from sunlight, and for a long time I thought our chemist did not recognize porphyria when it might be present, but eventually he demonstrated porphyrins in 3 cases of congenital porphyria with neurologic symptoms. We have been able to study 1 case exactly like that of the first man, and our observations were practically the same as those reported by Dr. Brunsting. Porphyria with photosensitivity must be latent for many years before giving rise to any symptoms on the skin. I should like Dr. Brunsting to point out the difference, if any, between porphyria with blisters and hyperpigmentation from congenital porphyria with neurogenic or other manifestations but no cutaneous manifestations.

DR. L. A. BRUNSTING, Rochester, Minn.: As a rule, in so-called porphyria, where the urine is port wine color and there are symptoms of abdominal colic or neurologic disturbances, there are relatively few changes in the skin and no photosensitivity. In the rare condition of congenital porphyria occurring in children, the skin bears the brunt of the disturbance. In the intermittent types such as those described here, of which we have seen some 14 examples in the past few years, the patient is usually in fairly good general health except for the skin, which shows the characteristic violaceous color of the exposed surfaces and a tendency for the surface to rupture and to blister spontaneously, especially under exposure to light. Occasionally acute and intermittent porphyria are combined, as in the young man presented. He showed a considerable amount of porphobilinogen. The role of the porphyrins in production of states of photosensitivity is still unsettled.

In this syndrome, too, there is some obscure relation to disease of the liver or some toxemia such as occurs in alcoholism or cirrhosis. On the whole, the prognosis in this group has been good. In the examination of cases of suspected porphyria, one does not often see the classic port wine urine. Porphyrins give a characteristic orange fluorescence, but this must not be confused with the coloring obtained from certain urinary pigments such as urofuscein or from riboflavin.

Exfoliative Dermatitis with Sensitivity to Light.

R. R. J., a 43 year old white man, moved from Kansas to Reno, Nev., in the summer of 1946. In the summer of 1947 he acquired a slight dermatitis of the ears which soon faded. In the summer of 1948 he had a plague of weeping

dermatitis on the back of his neck. The eruption spread to involve the ears, face and chest. Scratch tests done at this time showed numerous ± or 1 + reactions to such substances as sagebrush, apples and orchard grass. The patient noticed no sensitivity to food or substances with which he came in contact. The patient received local treatment in Reno, and in September 1948 he went to California for treatment. At that time he was found to be sensitive to all ointments. Potassium permanganate tubs were utilized, and most of the dermatitis subsided. In January 1949 the patient noticed that his skin flared in the exposed areas whenever he went outdoors.

The patient had had a dermatitis of the hands and arms as a child. The eruption appeared in the spring when the cows were shedding. There was no atopy in his family.

On May 15, 1949, he was seen at the Mayo Clinic, where he presented a weeping dermatitis of the face, ears, neck and hands, with milder dermatitis behind the knees. Tests for sensitivity to light were done, and the patient had a pronounced reaction to ultraviolet radiation with a lesser although still abnormal reaction to infra-red radiation. He manifested an eczematoid reaction four hours after a five minute exposure to sunlight. An attempt at a passive transfer reaction with use of the method described by Beale (*J. Invest. Dermat.,* January 1949) was unsuccessful.

The patient was found to be sensitive to cycloform preparations and other protective lotions. A diet eliminating green vegetables and the administration of tripelennamine (pyribenzamine®) seemed to decrease the sensitivity to light.

After improvement of the eczema, the patient was discharged as having atopic dermatitis with pronounced sensitivity to light.

He returned eighteen days later. He had acquired an acute exacerbation a few hours after arriving in Reno. Two tests for sensitivity to light were done after testosterone therapy, and the patient exhibited decreasing sensitivity to ultraviolet radiation. The reaction to infra-red radiation had disappeared. His skin condition has improved on local therapy.

DISCUSSION

DR. S. EPSTEIN, Marshfield, Wis.: This is a very interesting case of sensitivity to light. We recognize several distinct forms of pathologic sensitivity to sunlight: The main clinical manifestations are urticaria photogenica, with its urticarial sensitivity; prurigo aestivalis, which is probably a form of atopic sensitivity, and "eczema solare," or contact type solar dermatitis, which is apparently based on contact type epidermal sensitivity. One or more of these forms may be combined in the same patient. The present patient appears to be atopic, but the pictures of the clinical lesions and of the reactions to light tests are typical of contact dermatitis. When the patient exposed his hands to natural sunlight for a few minutes, four hours later he acquired an acute vesicular, weeping dermatitis. It seems to me that the sensitivity here represents a case of contact type sensitivity to sunlight.

What are the sensitizers in this type of photodermatitis? Localized lesions of contact type photosensitivity can be reproduced by the external application of photosensitizing substances, such as sulfonamides or photosensitizing plant extracts; however, in the generalized cases we must assume that the responsible agent comes from within. Except for cases caused by sensitivity to a drug, I do not know of one instance in which a sensitizer actually has been demonstrated. Even in cases which originally were connected with a sensitivity to a drug, such as an arsenical (Joun, M.: *Arch. f. Dermat. u. Syph.* **156**:355, 1928), photosensitivity

persisted for many months or longer, when one could not assume that the original drug was still a factor. One may assume in these instances that sensitivity may have developed to body-own proteins and that one is dealing with a form of auto-sensitization. Such a mechanism has been made plausible for some cases of urticaria photogenica, in which the sensitizers appear to be normal metabolites.

I have one question: This patient, like others of his type, apparently reacts to more than one wavelength, especially to erythema-producing rays. Has this patient been tested with roentgen rays and also alpha, beta and gamma rays?

DR. ROBERT R. KIERLAND, Rochester, Minn.: No, this patient has not been tested with other erythema-producing radiation.

DR. S. WILLIAM BECKER JR., Rochester, Minn. (by invitation): This patient had an extremely intense reaction to radiation. He was most sensitive to long wave ultraviolet but was also sensitive to infra-red and visible radiation. A dermatitis was produced by light which filtered through the towels used to demarcate the test area. Four hours after a five minute walk in the sunlight he manifested a weeping dermatitis of the exposed surfaces. He was sensitive to most ointments. The administration of tripelennamine (pyribenzamine®) lengthened the incubation period of light sensitization from four to nine hours. We also tried keeping the patient on a diet which contained no green vegetables, but this produced little improvement. The sensitivity to infra-red radiation has disappeared, but the patient still has a pronounced intolerance to the long wave ultraviolet radiation and direct sunlight, so that we have not changed his sensitivity much.

DR. L. A. BRUNSTING, Rochester, Minn.: At first, the patient seemed to have the usual problem of neurodermatitis or atopic dermatitis. It was only after a period of observation that it became apparent that he is sensitive to light, and at the present time this is the major source of his difficulty. In some such instances, a precipitating factor can be elicited. I recall the case of a man who became extremely sensitive to the sun after exposure to the juice of the gas plant (Dictamnus albus) in the course of his hobby as a gardener.

Disseminate Lupus Erythematosus.

Miss S. J. J., aged 21, was first seen by us in September 1948. Beginning in March 1947, she had had recurring periods of arthralgia, low grade fever and weakness, with two episodes of high fever and serious illness: The first, and milder, of these was in June 1947 and was precipitated by excessive exposure to sunlight. It was accompanied with an erythematosus eruption over the nose, cheeks and forehead, lasting for a few weeks only. This was the only cutaneous manifestation of her illness. The second serious febrile episode, in October 1947, was severe, but the patient felt much better for several months thereafter.

On her first admission here, in September 1948, she showed no skin lesions. There were many L. E. cells in the sternal marrow. The white blood cell count was 5,000, and the sedimentation rate, 103 mm. in one hour (Westergren). The Wassermann reaction was weakly positive; Hinton, positive; Kahn, 4+ with a titer of 32 units, and Kline, 2+. The patient was sent home with instructions to take vitamin E and potassium iodide.

During the past winter and spring she remained in bed, since even slight activity caused increased fever and joint pains. On three occasions she had a febrile reaction to the oral administration of paraaminobenzoic acid after first having tolerated it for a month.

On readmission here Aug. 9, 1949, she had mild fever, tachycardia, a sedimentation rate of 110 mm. and a few L. E. cells in her sternal marrow. Eight days

after admission she began to menstruate and her temperature rose. She had two chills on the following days, and for the next five days she was acutely ill, with a high fever. This gradually subsided by the tenth day, after which her pulse rate and temperature were definitely lower than they had been prior to the febrile episode. The white blood cell count, originally 6,700, fell to 1,500 during the fever and later rose to around 4,000. The sedimentation rate after the fever dropped to 20 mm. in one hour. Her blood pressure was found to be elevated after the fever, whereas previously it had been normal. No urinary changes have been noted.

Treatment during the febrile episode consisted of testosterone injections, administration of penicillin and the administration of 1,500 cc. of plasma and 1,000 cc. of whole blood during a five day period.

DISCUSSION

DR. MALCOLM M. HARGRAVES, Rochester, Minn. (by invitation): During the last four years we have been observing a phenomenon in the bone marrow preparations obtained from patients with acute disseminated lupus erythematosus which we believe is specific for this disease. On Jan. 21, 1948, Richmond, Morton and I published our first account of this phenomenon, the so-called L. E. cell (Hargraves, M. D.; Richmond, H., and Morton, R.: Presentation of Two Bone Marrow Elements: the "Tart" Cell and the "L.E." cell, *Proc. Staff Meet., Mayo Clinic* **23**: 25-26 [Jan. 21] 1948).

This cell undoubtedly represents a process which is going on in such bone marrows and is the end result of one of two things: either phagocytosis of free nuclear material with a resulting round vacuole containing this partly digested and lysed nuclear material or, second, an actual autolysis of one or more lobes of the nucleus of the involved cell so that it presents essentially the same appearance as a cell which has phagocytosed nuclear material. The L. E. cell is practically always a mature neutrophilic polymorphonuclear leukocyte. It seems obvious that the chromatin material is within a large phagocytic vacuole and all gradations of digestion of this material have been observed. While most of these cells characteristically show a homogenous, purple-staining mass in the vacuole there are instances in which the chromatin matter is visible. For this reason it is essential that this cell be differentiated from the tart cell described in our original paper. Ordinarily this can be accomplished by finding numerous L. E. cells in which the process of digestion has altered the appearance of this chromatin material, ranging from smoky remnants of "digested" material to relatively intact nuclei indistinguishable from the secondary nucleus of the tart cell.

The L. E. cell, we are sure, is the only result of a lytic-phagocytic phenomenon. Preparations stained with a specific nuclear stain (Feulgen's stain) show that the material in the vacuoles reacts as nuclear material would. Actual phagocytosis of this free nuclear material can be observed in any bone marrow where this process is at all active. One can observe numerous mature neutrophilic polymorphonuclear leukocytes attempting to pick up the same mass of material. In supravital preparations this phagocytic action has been observed with two or more neutrophils attempting to ingest one bit of nuclear material. When one of the cells has succeeded in ingesting it, the other cells have moved off as though the chemotactic attraction were now lost. These L. E. cells are commonly found in clumps in the fringe or edge of the marrow smear. This arrangement again is probably the result of the chemotaxis with the cells clumping about the nuclear material and being carried en masse to the fringe, as are other large cellular elements.

While Haserick and Sundberg (Haserick, J. R., and Sundberg, R. D.: The Bone Marrow as a Diagnostic Aid in Acute Disseminated Lupus Erythematosus. *J. Invest. Dermat.* **1**: 209-213 [Sept.] 1948) duplicated our experience, we received reports from others who were interested in this phenomenon but were unable to duplicate our work or observations. Inquiry revealed that the bone marrow preparations of these investigators were direct smears made at the time of sternal puncture. We then studied cases in which we had found these cells, employing both our usual technic and direct smears, and we too failed to find the L. E. cell when the bone marrow smear was a direct smear.

In our original paper we stated that we had never found the L. E. cell in the peripheral blood. After we had made the foregoing observations, however, it seemed reasonable to us that the phenomenon had not been observed in the peripheral blood because the material examined had been direct smears of blood elements, similar to direct smears of bone marrow. Consequently, we drew venous blood, added any of the anticoagulants, centrifuged the material and made smears from the buffy coat layer, and in cases in which results of examination of the bone marrow had been positive we observed the L. E. cell in small numbers.

The next obvious suggestion after these observations was that the material responsible for the nucleolysis, agglutination and phagocytosis might well be in the plasma of patients suffering from acute disseminated lupus erythematosus and that we could reproduce L. E. cells with the use of bone marrow from patients who did not have the disease named. Using plasma obtained from venous blood of patients with acute disseminated lupus erythematosus, we next put into the plasma bone marrow material obtained from patients who had various other diseases. We incubated the preparation at body temperature for a short time and then made concentrated preparations. Typical L. E. cells, as well as the phenomena of nucleolysis and agglutination, were observed.

These further observations on the L. E. cells would add weight to the hypothesis that Libman-Sacks disease, or acute disseminated lupus erythematosus, is the result of hypersensitivity or overreaction of the body defenses. The L. E. cell phenomenon is evidently immunologic, and considerably more study is required before any positive statements can be made regarding the mechanism concerned. However, I believe we can say that the L. E. cell is a specific indicator of the underlying process that produces clinical conditions such as those known as acute disseminated lupus erythematosus, lupus without cutaneous manifestations and Libman-Sacks disease. In the subacute or chronic phase the phenomenon may be lacking or difficult to demonstrate, and this fact suggests that the number of L. E. cells present, as well as the amount of agglutination of neutrophils about the chemotactic material, is in a way a measure of the titer of the circulating factor responsible for the production of the disease.

DR. M. R. CARO, Chicago (by invitation): Is the observation of these cells of any significance in evaluating the prognosis in any given case of lupus erythematosus?

DR. JOHN F. MADDEN, St. Paul, Minn.: I think that Dr. Hargraves has undoubtedly added a good deal to the means of diagnosing lupus erythematosus in the acute state. I think that the L. E. cell has been found in other diseases—I know especially of 1 case of multiple myeloma and that it has also been observed in leukemia. I think that the L. E. cell is an important factor leading to the diagnosis of acute lupus erythematosus in cases in which the diagnosis is in doubt. The L. E. cell may be one of the heartier types and more resistant.

DR. S. J. ZAKON, Chicago (by invitation): Do you also find the Hargrave cell in the chronic discoid type or in the subacute disseminated type?

DR. M. M. HARGRAVES, Rochester, Minn. (by invitation): In answer to Dr. Caro's question, I do not believe we are in a position to evaluate the prognosis, but I do believe that we can evaluate the acuteness of the process. Our experience to date would indicate that the more numerous the L. E. cells in the bone marrow preparations, the more acute the lupus erythematosus.

In reply to Dr. Madden, I am not sure that I can agree that the L. E. cells occur as an integral part of any other disease, but I will agree that they could occur associated with some other disease; however, personally, I believe that the L. E. phenomenon, whatever it is, is present in the patient with L. E. cells. My associates and I have observed at least 100 cases of myeloma since the one in which we made the original observation of L. E. cells and have never observed them in any other case. My assumption is that when L. E. cells are found in a disease other than lupus erythematosus the patient has both diseases.

In answer to Dr. Zakon's question, in the cases of chronic discoid lupus erythematosus in which the patients have been submitted to us for sternal aspiration, we have not found the L. E. cell phenomenon. In the subacute disseminated type, however, we have found a variable number, and, again, I think the observation depends entirely on the acuteness of the process.

DR. ISADORE FISHER, Minneapolis: We had occasion to recheck a patient who had recovered from acute lupus erythematosus approximately four years ago. The patient felt relatively well except for a tendency to tire easily. She had no fever, anemia, arthralgia or abnormalities of the urine. Reexamination of the bone marrow by Dr. Dorothy Sundberg revealed the presence of the L. E. (Hargrave) cell in the bone marrow four years after the original acute episode. This account may answer the question as to whether or not the L. E. cells have been found in patients who have recovered from lupus erythematosus.

Familial Benign Chronic Pemphigus (Hailey and Hailey); Bullous Darier's Disease.

Mrs. A. S., a 49 year old housewife, first was seen by us on Aug. 24, 1949, with a history of a recurrent exudative and vesicular dermatitis for twenty years.

DISCUSSION

DR. S. W. BECKER, Chicago (by invitation): Dr. Obermayer and I treated this patient for two and one-half years. I presented her at the Chicago Dermatological Society on Oct. 21, 1942, as having dyskeratosis bullosa (so-called benign familial pemphigus). While attention has been focused on this disorder only recently, the same or a similar disorder was reported by Zweig (Zweig, L.: Ueber einen Fall von Epidermolysis bullosa hereditaria, *Arch. f. Dermat. u. Syph.* **125:** 1, 1920). A man had had "chronic pemphigus" since youth, severer in summer than in winter. On the basis of crusted and bullous lesions on various parts of the body, a diagnosis was made of dermatitis herpetiformis. This diagnosis was later changed to epidermolysis bullosa hereditaria. Thirteen of 22 persons in four generations, only 2 of whom were women, had the disorder. Sachs, Hyman and Gray (Sachs, W.; Hyman, A. B., and Gray, M. B.: Epidermolysis Bullosa, A Recently Described Variant, ARCH. DERMAT. & SYPH. **55:**91 [Jan.] 1947) stated that there was not a single patient with true Darier's disease, in their series, and so I cannot subscribe to the designation "bullous Darier's disease," as used by Pels and Goodman. I believe the condition presented here is an entity.

DR. M. R. CARO, Chicago (by invitation): The response to treatment cannot be used as an aid in differential diagnosis, for some patients may respond for a while to the administration of vitamin A, 30 per cent sulfur or roentgen rays. This

condition should be considered a distinct disease of unknown etiology. Its clinical appearance, histologic features and intermittent course with spontaneous remissions separate it from any known connection with any other cutaneous disorder.

Eosinophilic Granuloma with Diabetes Insipidus.

G. J. R., aged 42, an unemployed salesman of Jewish extraction, was first seen at the Clinic on Aug. 30, 1949, with the present complaint of exquisite pain and tenderness of the perianal area. Approximately twenty years ago he had extreme polydipsia and polyuria and a diagnosis of diabetes insipidus was made; the symptoms have been controlled with daily injections of beta-hypophamine (pitressin®). There have been no other signs of pituitary involvement, and the patient has a normal, healthy well developed 9 month old infant. Nine years ago he consulted his dentist because of the development of peculiar "teat-like" projections from the gum, palate and buccal membrane. There was also an overgrowth of the gum tissue around the lower teeth and the upper molars. Shortly afterward, painless, shallow ulcerations appeared on the buccal membrane. In the course of the next few months there was a gradual shrinking of the entire lower gum and a loss of all the lower teeth. A biopsy of these "teat-like" projections was interpreted as "unclassified malignant neoplasm." The upper incisors and canines have not become involved in the process.

Four years ago, after the onset of the mouth lesions, the patient acquired a painful fissure and fistula in ano in the site of a granulomatous lesion of the perianal area. This lesion was removed surgically, and afterward a painful abscess developed. A pathologic diagnosis of Schüller-Christian's disease or a lipid-containing reticuloendothelial granuloma was made of the perianal lesion and the mouth lesions (in retrospect). The perianal abscess has never healed completely, and a painful stricture developed.

A course of fractional roentgen irradiation was given to the perianal area in 1945-1946 without improvement.

Physical Examination.—Mouth: There is absence of the lower teeth and upper molars with complete atrophy of the lower gums. Several small ulcerations are present on the left buccal mucosa.

Proctoscopic and Rectal Examination: A perianal ulceration extends part of the 5 to 6 cm. from the anal verge and around the entire circumference of the anal orifice. The bed of the ulceration is moist and purulent, and the edges are rolled and firm. The anus and rectum are normal, but there is a contracture immediately adjacent to the anal verge which is painful and tender.

Laboratory Examinations.—The results of laboratory examinations were normal.

Pathologic Report.—Mouth: Eosinophilic granuloma with an associated pronounced epithelial hyperplasia (benign penetrating epithelium) was present.

Perianal Area: Eosinophilic granuloma was present.

DISCUSSION

DR. HAMILTON MONTGOMERY, Rochester, Minn.: There have been several specimens for biopsy on this case, all of which have shown varying degrees of eosinophilia. There have not been areas of necrosis in the tissue, which Sidney Farber emphasized as one of the histopathologic features of eosinophilic granuloma. This patient has diabetes insipidus but no evidence of any bone lesions. I would prefer to regard the condition, for the time being, as a nonspecific granuloma with eosinophilia rather than classify it as eosinophilic granuloma of the skin and bone related to Hand-Schüller-Christian disease and Letterer-Siwe disease. Cases of eosinophilic granuloma of the skin alone are apparently another condition, varying

from the cases that Weidman reported, which might be regarded as atypical Hodgkin's disease or other forms of lymphoblastoma, to the case reported by Lewis, which might be regarded as akin to a periarteritis nodosa and which was apparently on an allergic basis.

DR. MARCUS R. CARO, Chicago (by invitation): The section that I examined showed a great number of eosinophilic cells.

Tabetic Form of Dementia Paralytica with Noduloulcerative Syphiloderm of the Face.

F. T., a white woman aged 58, was first seen in the Dermatology Section on Aug. 23, 1949, because of an asymptomatic eruption on the face of four years' duration. She had also had some difficulty in walking for the past three years.

Twenty years ago, because of a vaginal ulcer, she was given 4 weekly intravenous injections. She never had an examination of the blood or spinal fluid for syphilis, nor was further antisyphilitic treatment given. Three years ago the eruption on the face was diagnosed as "psoriasis" and she was given 12 intravenous injections of a gold preparation without effect.

Physical examination reveals symmetric, indurated, nodular, annular plaques on the face with peripheral activity and central atrophy and scarring. There is a "saddle nose" deformity and a perforated nasal septum.

Examination of the blood revealed a 4+ reaction to the Kahn test, with a titer of 256 Kahn units, a 4+ reaction to the Kline test, a positive reaction to the Hinton test and strongly positive reactions to the Kolmer serologic test for syphilis. The spinal fluid examination showed a strongly positive reaction to the Kolmer test (44444), 280 mg. of protein per hundred cubic centimeters, 155 polymorphonuclear cells and 56 lymphoctyes per cubic centimeter and a colloidal gold curve of 5555432100.

A biopsy specimen taken from the left cheek showed the histologic picture of a tuberculoid syphiloderm.

On August 29 treatment was instituted and consisted of the oral administration of aureomycin capsules, 250 mg., every six hours. Except for slight nausea the patient has shown gradual improvement on this regimen.

DISCUSSION

DR. HAMILTON MONTGOMERY, Rochester, Minn.: One of the purposes for presenting this patient was that the specimen for biopsy showed all the features of lupus vulgaris and did not show a plasma cell infiltrate about thickened blood vessels at the periphery of the lesion such as one usually sees in syphiloderms, giving a tuberculoid-like reaction. Histopathologic diagnosis in this case, therefore, would be lupus vulgaris were it not for the correlation of clinical features and the response to treatment.

DR. MARCUS R. CARO, Chicago (by invitation): I recall seeing a patient about fifteen years ago with an extensive ulceration involving the entire center of the face, with destruction of the nose. Repeated serologic tests of the blood for syphilis had given negative reactions, and the woman had received many forms of treatment, including roentgen rays, radium, electrosurgical treatment and topical applications. Oral administration of potassium iodide and mercury and chalk produced rapid healing of the ulcerated patch, at which time the Wassermann reaction of the blood became positive.

DR. JOHN J. SEVENANTS, La Crosse, Wis.: What are the doses of aureomycin?

DR. ROBERT R. KIERLAND, Rochester, Minn.: We use a daily dose of between 2 and 4 Gm., and courses of therapy last from two to three weeks. I do not know what the best dose is for these patients.

DR. JOHN SCHMIDT, Duluth, Minn.: What have been the reactions you have observed following the prolonged use of aureomycin?

DR. ROBERT R. KIERLAND, Rochester, Minn.: Clinically, the results from aureomycin seem equivalent to those produced by penicillin in patients with syphilis of the central nervous system. Of course our series is not yet large enough nor have we observed the patients long enough to make sure of the ultimate results, but at least the early results are as good. The improvement noted in the examinations of the cerebrospinal fluid is as rapid as with penicillin and appears before the beneficial clinical results.

DR. JOHN SCHMIDT, Duluth, Minn.: We have recently seen 2 patients who showed glossitis, keratosis pilaris and photosensitivity following one or more months of continuous oral treatment with aureomycin. The picture suggested vitamin A and B deficiencies. This response can be explained by the sterilizing effect which aureomycin has on the intestinal bacteria, the bacteria concerned with synthesis of the vitamin B complex thus being affected. We obtained prompt relief of the pellagra-like eruption by parenteral administration of nicotinamide.

Rosacea-like Tuberculid.

J. W. C., a 58 year old housewife, was first admitted to the Clinic on Nov. 10, 1948, because of a subacute dermatitis limited to the face, which was thought to be a contact dermatitis. Three days later, after the use of wet dressings and a bland ointment locally, the acute reaction subsided and there remained numerous minute, translucent yellowish papules which had an apple jelly appearance under the diascope. A diagnosis of lupus miliaris disseminatus facie or rosacea-like tuberculid was considered clinically. Bland local treatment was continued. On November 18 a specimen was removed for biopsy and a diagnosis of rosacea-like tuberculid was made. A test with single strength tuberculin elicited a negative reaction. The roentgenogram of the chest and urinalysis revealed normal conditions.

The eruption continued to progress over the face despite treatment, and on Jan. 14, 1949, the administration of dihydrostreptomycin and vitamin D_2 was started and continued for two months. There was little change in the eruption during this period.

The patient returned on May 3, and the facial eruption was worse. At her last visit, on May 12, the eruption was unchanged from the time of her original visit.

DISCUSSION

DR. HENRY E. MICHELSON, Minneapolis: The problem of persistent papular eruptions of the face that resemble both rosacea and tuberculosis is a difficult one. Since this diagnosis has been introduced to the dermatologic world it has taken a good hold, and I am afraid it will be hard to break the habits formed. I am even doubtful that there is such a thing as rosacea-like tuberculid. From my point of view there is nothing characteristic about it, either morphologically or microscopically.

DR. ROBERT R. KIERLAND, Rochester, Minn.: What would you call this condition?

DR. HENRY E. MICHELSON, Minneapolis: Resistant papular dermatitis of the face with rosacea-like character.

DR. PAUL A. O'LEARY, Rochester, Minn.: I agree with Dr. Michelson's suggestion; however, I also believe that each patient who is suspected of having a tuberculid of the face, diagnosed on a clinical and/or pathologic basis, should have a course of treatment with a sulfur preparation before a diagnosis of tuberculid is made. Not infrequently a favorable therapeutic effect warrants a change in the diagnosis.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I am in essential accord with Dr. Michelson. Here at the Clinic we take specimens for biopsy in cases of rosacea only when there is a suspicion that the patient may have rosacea-like tuberculid. In only a small percentage of the cases has biopsy shown a specific tubercle formation. The patient presented did not respond to treatment for rosacea and has, I believe, rather typical histologic features of tuberculosis. In rosacea-like tuberculid, the histopathologic picture frequently resembles that of sarcoid in that the tubercles are composed almost entirely of epithelioid cells. Just as there is increased evidence that sarcoidosis is not true tuberculosis, so must we remain open-minded regarding a nontuberculous etiology for rosacea-like tuberculid.

Erythema Induratum with Untoward Reactions from Paraaminosalicylic Acid.

Miss Y. B., a 30 year old French Canadian woman, came to the Clinic because of recurrent ulcers of the lower half of the legs and of the feet for the past thirteen years. Three years ago the right leg was amputated below the knee because of severe ulceration. The ulcers had developed from tender purplish nodules which usually appeared during a menstrual period. Previously the patient had received streptomycin intramuscularly for five months. During that same period she was given vitamin D_2 for three weeks. A severe drug reaction was said to have resulted from the use of both of these drugs. Additional treatment which she had received included the administration of penicillin, potassium iodide, vitamin A and ultraviolet and roentgen radiation, a left lumbar sympathectomy in 1948 and a bilateral subtotal thyroidectomy in 1948.

The results of laboratory tests here were essentially normal. Guinea pig inoculation was negative for tuberculosis on two occasions. Biopsy of a nodule showed erythema induratum.

Treatment here included roentgen ray therapy, the intravenous administration of oxophenarsine (mapharsen®), the administration of paraaminosalicylic acid, foreign protein fever therapy, the administration of vitamin E, bed rest and the application of pressure bandages. Paraaminosalicylic acid treatment had to be discontinued after eleven days because of sudden fever and a pruritic erythematous drug eruption. The dermatitis medicamentosa promptly disappeared after the administration of this drug was stopped. Since the first supply of paraaminosalicylic acid was obtained from an English firm, a second supply was obtained from an American house in the hope that its composition would be slightly different. However, dermatitis medicamentosa promptly reappeared when the drug was given five days later.

A new tender nodule developed on the left leg during the patient's last menstrual period. About a week ago it also became ulcerated.

DISCUSSION

DR. ROBERT R. KIERLAND, Rochester, Minn.: At the present time this patient exhibits erythema induratum which is healing. We have treated this patient with paraaminosalicylic acid, from which she acquired a dermatitis medicamentosa of the scarlatiniform type and drug fever. This subsided rapidly. To date we have had

4 patients who have exhibited types of dermatitis medicamentosa when given this drug, and 2 of these 4 patients had drug fever as well. We have treated over 100 patients with various types of tuberculosis with paraaminosalicylic acid, and so it would seem that the incidence of untoward reactions lies somewhere between 2 and 4 per cent.

DR. PAUL A. O'LEARY, Rochester, Minn.: I had hoped to present at this meeting a male adult with nodular lesions of the legs who illustrates the difficult diagnostic problem such nodules present. The clinical picture may suggest thrombophlebitis, erythema nodosum, periarteritis nodosa, panniculitis or nodular vasculitis. Physicians who have had considerable experience with these conditions frequently differ in their clinical interpretation of these lesions. It is seldom that all are in diagnostic accord. The histopathologic study may be equally misleading if the biopsy is done with a skin punch, because in the removal of such a small piece of skin the fundamental pathologic process may be missed and an erroneous diagnosis made on the secondary pathologic changes. Accordingly a wide excision of the nodule with the study of serial sections is more likely to result in accurate diagnosis. I believe the patient under discussion has had erythema induratum, and amputation of the right leg seems to me a very radical method of treating this disease.

DR. J. B. HOWELL, Dallas, Texas (by invitation): What features are necessary in the nodular lesions of the legs, clinically and pathologically, before a diagnosis of nodular vasculitis may be made?

DR. PAUL A. O'LEARY, Rochester, Minn.: The term nodular vasculitis was coined to include the nodular lesions of the thighs as well as the lower parts of the legs in middle-aged adults, usually women. In patients with this condition evidence of tuberculosis as determined by histopathologic examination, animal inoculation studies and clinical surveys has been negative. The lesions are not as large or indurated as those of erythema induratum, and they recur in crops, with periods lasting several months when the patients are free of the nodes. Hypertension in moderate degrees has been a most consistent observation in these patients.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: In regard to taking specimens for biopsy of the legs, we have no hesitancy in taking large and deep excision biopsy specimens and find that the biopsy wound heals just as well there as in other parts of the body. Sometimes, where part of an ulcer has been excised, the healing is even better than if one attempted to obtain healing by local applications. In regard to the diagnosis of nodular vasculitis, the condition is seen predominantly in middle-aged women. Some of the nodules may ulcerate. The individual lesions last much longer than the lesions in erythema nodosum. The lesions are not transitory and painful, as they usually are in erythema nodosum. There is no history of medication. There is no deep ulceration or true tubercle formation such as is seen in erythema induratum. Although erythema induratum presents a rather classic picture clinically, in a large series of cases I was able to find definite tubercle formation in only 75 per cent of the patients.

Psoriasis: Treatment with Cortisone and ACTH.

Miss S. R., aged 25 years, was received at the Clinic on Sept. 9, 1949, for treatment of psoriasis. Previously she had been a patient of ours and had been treated with tar and ultraviolet radiation, with good results.

Summary of Recent Course.—Psoriasis had recurred in April 1946, four months after the last hospitalization. The patient was admitted in May 1949 for arthritis. Psoriasis was widespread and consisted of large gyrate plaques.

Cortisone was given from May 21 to July 2. During the first week or so improvement was moderate in the psoriasis and considerable in the arthritis. Then the skin began to get worse. After treatment with cortisone was stopped, the lesions became worse than at the beginning of therapy.

ACTH was given from July 30 through August 26. The dosage up to August 10 was 80 mg. daily. On this dosage little change was noted in the skin. The dose was increased to 160 mg. daily, and by the end of thirty-six or forty-eight hours the patient stated that her skin was improved. Improvement was also noted in forty-eight hours by her physicians. The lesions continued to improve—first in amount of redness, then in scaling and then in infiltration. By August 27 the lesions were not recognizable as psoriasis. Many areas had cleared altogether except for a residual staining. Arthritic symptoms were much improved on ACTH therapy.

After the administration of ACTH was stopped, acneform lesions were noted on the forehead and an increased amount of hair was noted on the upper lip. The arthritis remained asymptomatic, but the patient has had some pain in the past few days.

During the first week after the end of treatment there was no return of psoriasis, but in the second week (i. e., the past week) there has been a very rapid return of skin lesions on the forearms, legs and scalp.

White Sponge Nevus: Moniliasis?

E. L. H., a girl aged 15, since the age of 3 days was noted to have white spongy plaques on the buccal, oral and lingual mucosa. The lesions have disappeared spontaneously on a few occasions and on one occasion following intramuscular injections of penicillin. There was no change at the time of the menarche. No other skin lesions have been noted. Examination of the vulva and vagina revealed no abnormality.

The patient was seen here on June 24, 1949, when a biopsy revealed changes consistent with the white sponge nevus of Cannon. Examination of a specimen treated with potassium hydroxide did not reveal fungi. However, cultures were positive for Candida albicans.

The patient's general health has been good except that she is 30 pounds (14 Kg.) underweight. Results of laboratory tests were normal.

DISCUSSION

DR. HAROLD G. RAVITS, St. Paul, Minn.: The only comment I can make is that Candida albicans is often found in the mucous membranes as a saprophyte. I do not know whether the observation of it means anything in this patient. When does a saprophyte become a pathogen, and why isn't there a response to therapy?

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I made the histopathologic diagnosis of white sponge nevus before I saw the patient because of the peculiar spongy appearance of the corneal layer. Moniliae may be found as secondary invaders in various pathologic processes. This girl had lesions in her mouth since three days after birth, which observation would speak against the diagnosis of moniliasis. Furthermore, she does not have any vulvar lesions.

DR. FRANCIS W. LYNCH, St. Paul, Minn.: I regard this condition as a white sponge nevus but believe that this is the disorder described in former years as leukokeratosis (oris, buccalis, etc.), not related to leukoplakia.

Prurigo Nodularis.

S. E., a 64 year old man, was first seen by us in 1938. His skin was normal at that time except for a keratosis senilis on the dorsum of the left hand. He returned in 1942 with a complaint of a very pruritic papular eruption since August 1941 involving the elbows, gluteal regions and pressure areas of the palms and soles. The lesions began as minute papules and enlarged slowly and persisted. There were never any vesicles or pustules. No exacerbation followed ingestion of potassium iodide, and the reaction to a patch test with potassium iodide was negative.

After the patient's dismissal more lesions appeared, none of the old disappearing, and at the present time he has returned because of his pruritic eruption. Except on the head, there is generalized involvement with scattered superficial hyperkeratotic excoriated nodules and papules. He states that warm weather and emotional tension increase the pruritus with resultant secondary increase in the size of the lesions. There is nothing in the general examination to indicate a malignant condition. Results of routine laboratory work were noncontributory.

DISCUSSION

DR. HENRY E. MICHELSON, Minneapolis: I am sure the diagnosis of prurigo nodularis takes in quite a number of conditions. To my mind, the true prurigo nodularis of Hyde is characterized microscopically by hyperkeratoses and practically no infiltrate. You all know the clinical characteristics. I thought that in the present case there was a great deal of infiltrate, which made me doubt the diagnosis. I would try penicillin and nicotinic acid therapy although that treatment has not been satisfactory for lichen planus in my hands.

DR. MARCUS R. CARO, Chicago (by invitation): I agree with the diagnosis of prurigo nodularis in this case both clinically and with regard to the section. In 2 patients whom I studied the lesions were identical with these and the sections showed foci of dense cellular infiltrate deep in the corium. Ordinary treatment, including roentgen rays, sedatives, and topical applications, was of no value. Lesions could be destroyed, however, by deep burning with the electrocautery, and I should like to suggest that form of treatment in this case.

Atopic Dermatitis with Melanosis: Sclerodermatomyositis.

W. G. P., a 34 year old housewife from the Panama Canal Zone, was well until the birth of her third child, in 1945. At that time she had pruritus of the eyelids which lasted for ten days. She then experienced a rather severe pruritus of the abdomen and flanks which was accompanied with hyperpigmentation following the scratching. Pruritus gradually spread to the crural areas and, in the past year, generally over the body. The hyperpigmentation following the same course and sharply limited to the pruritic areas now involves the whole body except the face, palms, soles and mucous membranes.

Eleven months after the onset of the pruritus, the patient had a temperature of 105 F. and was hospitalized. A diagnosis of typhus was made, and the patient was discharged after treatment. An erythematous macular eruption was present during this febrile episode.

One and one-half months later, the patient had a low grade fever, but there was no elevated temperature when she was hospitalized. In November 1947 the patient again had a fever. She was hospitalized, given penicillin and then advised to go to New York. At this time she began to notice weakness, particularly of the legs. Weakness has improved during the last year, but the patient cannot

rise from a squatting position, climb a tall step or sit up in bed unaided. After a workup at Presbyterian Medical Center, which apparently included tests for Addison's disease and two biopsies, the patient was told that she had dermatomyositis. She says that she has had a low grade fever (99 to 101 F.) since November 1947.

One year ago she was hospitalized because of an infected ankle. She was given penicillin and had pronounced pruritus with a generalized exudative dermatitis. The patient states that this episode was a great strain on her and that since that time she has had episodes of tenseness during which picking at her skin relieved her.

There is no history of muscle tenderness or difficulty in swallowing. All other systems are normal except that there has been amenorrhea the last two months. There is no history of atopy in the patient or family.

The patient has used iodides, vitamins and one month of testosterone therapy with no benefit. For the past year she has been using tripelennamine (pyribenzamine®) to control pruritus. She has pronounced itching and "peculiar feelings" if she omits this drug.

The observations on general physical examination are normal except for muscle weakness.

The skin exhibits a pronounced diffuse hyperpigmentation from the upper portion of the neck to the ankles, sparing the palms, the face (which is only slightly pigmented), the soles and the mucous membranes. There is generalized lichenification and excoriation, more noticeable in the flexors. There are numerous scars over the body. There is a suggestion of pinching of the nose and tightness about the mouth.

In laboratory tests the amount of hemoglobin, red blood cell count, white blood cell count, differential count, urine and Kline reaction were found to be normal. There was no melanin in the urine. The sedimentation rate was 50 mm. per hour. Dental and chest roentgenograms revealed normal conditions. Fluoroscopy of the esophagus showed delayed peristalsis. An electromyogram of the left trapezius muscle showed changes consistent with dermatomyositis.

DISCUSSION

DR. S. W. BECKER, Chicago (by invitation): I think the chief feature here is that this patient stated that as a girl, before she had this dermatitis, she tanned in the sun and did not burn. Her eyes are not a dark brown. I think there is a great deal of variation in the individual and that many cases of severe melanosis occur only in persons who have had a tendency to tan before acquiring the dermatitis.

DR. PAUL A. O'LEARY, Rochester, Minn.: This patient had been sick for four years. A biopsy specimen from a thigh muscle taken elsewhere did not show significant muscle changes; although the muscle weakness is of four years' duration, the involvement seems to be primarily in the shoulder girdle group, so that a biopsy specimen taken from the muscle not showing clinical evidence of involvement would not reveal any significant pathologic changes.

DR. WILLIAM G. BROCK, Winnipeg, Manitoba, Canada: I could not see any clinical signs of dermatomyositis in this patient.

DR. T. B. FITZPATRICK, Rochester, Minn. (by invitation): We have recently seen pronounced generalized melanosis in patients with generalized scleroderma. The pigmentation is often of such intensity that a diagnosis of Addison's disease is entertained. These patients have a very low amount of 17-ketosteroids and pronounced weakness. However, the blood pressure is usually normal, and the

laboratory data other than for the 17-ketosteroids are not consistent with Addison's disease. This patient has very little cutaneous sclerosis, and it is unlikely that the melanosis can be explained on the basis of scleroderma.

Systematized Amyloidosis.

A. L. F., a 54 year old man, was well until three and one-half years ago, when he noted crumbling of the finger nails. He slowly acquired "white lines" on his hands and in the folds of the skin. A year and a half ago he noted thickened areas of skin on his finger tips which he thought were callosities. He then noted a diffuse and patchy loss of hair on his scalp. Eight months ago he began to complain of puffiness of his face and, during the cold winter months, noted triphasic color changes of his hands after exposure to cold. About this time he noted weakness for the first time and began to complain of dryness of the mouth, moderate difficulty in swallowing and swelling and stiffness of his tongue, causing a thickness in his speech. Since then all symptoms and signs have slowly progressed and, in addition, he has noted an easy bruising of his face and infiltration of the skin over spinous processes of the back and buttocks.

Previous treatment had consisted of the administration of bismuth sodium triglycollamate (bistrimate®), dihydrotachysterol (A.T.10), thyroid and vitamin A.

Congo red dye injected locally was retained in the infiltrated plaques; laboratory examinations, including roentgenologic examination of the esophagus, chest and right hand, revealed an essentially normal condition. The basal metabolic rate was reported as —6, and the electrocardiogram revealed the following factors: sinus tachycardia with a rate of 107; low amplitude of the QRS complex in leads I, II and III; left axis deviation; P-R interval, 0.20 to 0.22 seconds; positive T and absent R wave in lead V_1; positive T wave in lead V_3, and positive T wave in lead V_5.

Examination of the urine revealed a grade 2 albuminuria with occasional casts. Red and white cell counts and the amount of hemoglobin were within normal limits. The sedimentation rate was normal. The flocculation test for syphilis was negative. The total protein was 5.3 mg. per hundred cubic centimeters.

Results of investigation for evidence of multiple myeloma, including sternal biopsy, roentgenologic examination of the skull and examination of the urine for Bence Jones protein, were all negative.

DISCUSSION

Dr. Maurice J. Reuter, Milwaukee (by invitation): I had the opportunity of seeing this man about one and a half years ago, and at that time he had erythema and infiltration or sclerosis of the chin, cheeks and upper lip with involvement of the distal portion of the fingers and deformity of the nails. There was a history of color changes in the fingers suggesting Raynaud's phenomenon. There were no other changes at that time. We thought the condition was probably the syndrome Dr. O'Leary has called to our attention, namely acrosclerosis. A biopsy was done. I do not recall the microscopic observations, but we must have thought the picture was consistent with scleroderma or acrosclerosis because this diagnosis was made. No special stains were done, as amyloidosis was not even considered.

Dr. Ruben Nomland, Iowa City (by invitation): In a number of ways this man is a little different from the patients Drs. Brunsting and MacDonald (Brunsting, L. A., and MacDonald, I. D.: Primary Systematized Amyloidosis with Macroglossia: A Syndrome Related to Bence-Jones Proteinuria and Myeloma: *J. Invest. Dermat.* **8:** 145 [March] 1947) reported on several years ago in whom

lesions of the skin clinically were very superficial and consisted of translucent papules. In the present case there was a localized amyloid process just below the epidermis and there are systematized amyloidosis changes on the tongue. I am sure Dr. Michelson could say more about this subject than I could. The locally injected congo red was still apparent in the buttocks although the test was done many weeks ago.

DR. HENRY E. MICHELSON, Minneapolis: Localized amyloidosis is common in some domestic animals. It might be well to keep that in mind for investigations.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: The hemorrhagic tendency in these persons is probably explained on the basis of fragility of the vessel walls as the musculature becomes replaced by deposits of amyloid. In the examination of this patient there was no Bence Jones protein found in the urine; neither were myeloma cells found in the sternal marrow.

A Case for Diagnosis: Colloid Milium?

D. E. O., a 42 year old housewife, was seen because of a hemorrhagic eruption of four years' duration. The dermatosis began as purpuric areas on the eyelids with involvement of the inguinal region within one year and gradual spread to the neck and axillas. The lesions continued to increase in number and two years ago began to involve the mucous membranes of the mouth. The patient states that slight trauma, such as riding in an automobile, will cause hemorrhage. She had a proctoscopic examination ten days ago which was followed immediately by edema and ecchymosis of the periorbital regions. She has also had pains in the legs and edema at the end of the day since 1947. According to the patient, the hemorrhages occur first and are followed by the brownish to whitish papules. Except for slight fatigue, she feels well generally.

Results of extensive laboratory procedures have been essentially normal. The more pertinent results are as follows: prothrombin time, 20 seconds; serum proteins, 5.6 Gm. per cent; ascorbic acid, 0.8 mg. per cent (normal 0.4 to 1.0), and sedimentation rate, 30 mm. per hour.

There is no family history of skin diseases or bleeding tendencies.

Physical examination reveals many purpuric and ecchymotic lesions on the ears, chin, mouth, lips, eyelids, neck, shoulders, buttocks, perineum, inguinal region and genitalia. In these areas also are many pale to tan flat-topped, shiny papules pinhead to 3 mm. in diameter. No fluid exudes on puncture of the papules. The remainder of the physical examination revealed an essentially normal condition.

Treatment in the past has consisted of the administration of vitamin K, rutin and antihistaminic drugs, all of no avail.

Histopathologic studies of an excised papule showed colloid milium.

DISCUSSION

DR. ROBERT R. KIERLAND, Rochester, Minn.: This patient presents the hemorrhagic tendency which Dr. Brunsting just discussed in relation to amyloidosis. The question is whether we are dealing with colloid milium, systematized amyloidosis or something entirely different.

DR. RUBEN NOMLAND, Iowa City (by invitation): I do not know what the patient has. I saw the stains, but I did not see any special stains that showed amyloid.

DR. HENRY E. MICHELSON, Minneapolis: I was unable to make any diagnosis for this patient. I do not know what the condition is and should be most curious to find out after a diagnosis is made.

DR. FRANCIS W. LYNCH, St. Paul, Minn.: I think this might be amyloidosis with papular lesions of the type seen around the eyes in cases of systematized amyloidosis. Colloid milium has been said to improve with ascorbic acid therapy. I cannot make a diagnosis.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: Sections treated with Van Gieson stain revealed colloidal changes such as are seen in colloid milium. Clinically, I do not think this patient has colloid milium and I do not think that we selected the proper region for biopsy.

Urticaria Pigmentosa: Large Nodular Type.

D. R., a healthy boy aged 4½, of dark complexion and of Syrian parentage, was noted to have dark subcutaneous nodules at birth. Bullae also appeared on the summit of many of the lesions. When the child was 7 years of age, the bullae began to disappear and the nodules had been decreasing in size.

The child was first seen by us in November 1946. The twenty-five lesions at that time were all large nodules. Since no urtication resulted when the lesions were stroked and since the polychrome methylene blue stain was negative for mast cells with metachromatic granules, the diagnosis of urticaria pigmentosa was dismissed. However, on subsequent staining with the Giemsa technic the diagnosis was established. Typical mast cells with metachromatic granules established the diagnosis of urticaria pigmentosa.

The patient was again seen after a lapse of two and a half years. On examination in March 1949 the total number of lesions had remained but the infiltration had disappeared in about a third of the lesions. No urtication resulted when the lesions were stroked.

The results of the Quick determination of prothrombin time and the prothrombin consumption test performed on Sept. 10, 1949 were within normal limits.

DISCUSSION

DR. S. W. BECKER, Chicago (by invitation): I have never seen this type before, except in this patient.

DR. RUBEN NOMLAND, Iowa City (by invitation): I think this child presented three unusual features of urticaria pigmentosa: (1) the lesions were much larger than normal; (2) there was a blistering eruption early in infancy, and (3) the lesions were definitely infiltrated and nodular.

DR. ROBERT R. KIERLAND, Rochester, Minn.: This patient presents unusual features of urticaria pigmentosa: first of all, the appearance at birth and, secondly, the nodular lesion which Finnerud discussed a number of years ago. The lesions are subsiding spontaneously. It is of interest that the mast cell is a source of heparin but this patient has exhibited no unusual bleeding tendency. This patient will be the subject of a paper by Dr. Stegmaier and me (ARCH. DERMAT. & SYPH. **62:** 28 [July] 1950).

Bullous Lichen Sclerosus et Atrophicus.

Mrs. T. M. H., a 69 year old white woman, was first seen at the Clinic on June 28, 1949, because of an inflammatory dermatitis under the breasts and extending over the lower part of the abdomen.

Approximately one year ago she noted fissuring of the skin beneath the breasts, with development of bullae. Six months later, in December 1948, she noted white sclerotic lesions in the same area and again had bullae, which lasted two

weeks. In April 1949 she experienced a third episode of bleb formation, which lasted only a week. No change was noted in the sclerotic areas after the disappearance of the blebs.

Examination on June 28, 1949, revealed submammary intertrigo with secondary infection and inflammatory reaction extending to the under surface of the breasts superiorly and over the abdomen inferiorly. Under the left breast and over the presternal area there were large bullae beneath which was an ivory-colored sclerotic type of skin. At the border of the indurated plaque are individual white pearly lesions.

Present about the vulva and anus is the symmetric "keyhole" eruption with lichenoid white papules at the border.

Incidental tinea versicolor has been present as long as the patient can remember.

DISCUSSION

DR. CARL W. LAYMON, Minneapolis: Many of us have seen lichen sclerosus in the same person who has clinical morphea. I think the appearance of the vulva was more that of lichen sclerosus et atrophicus.

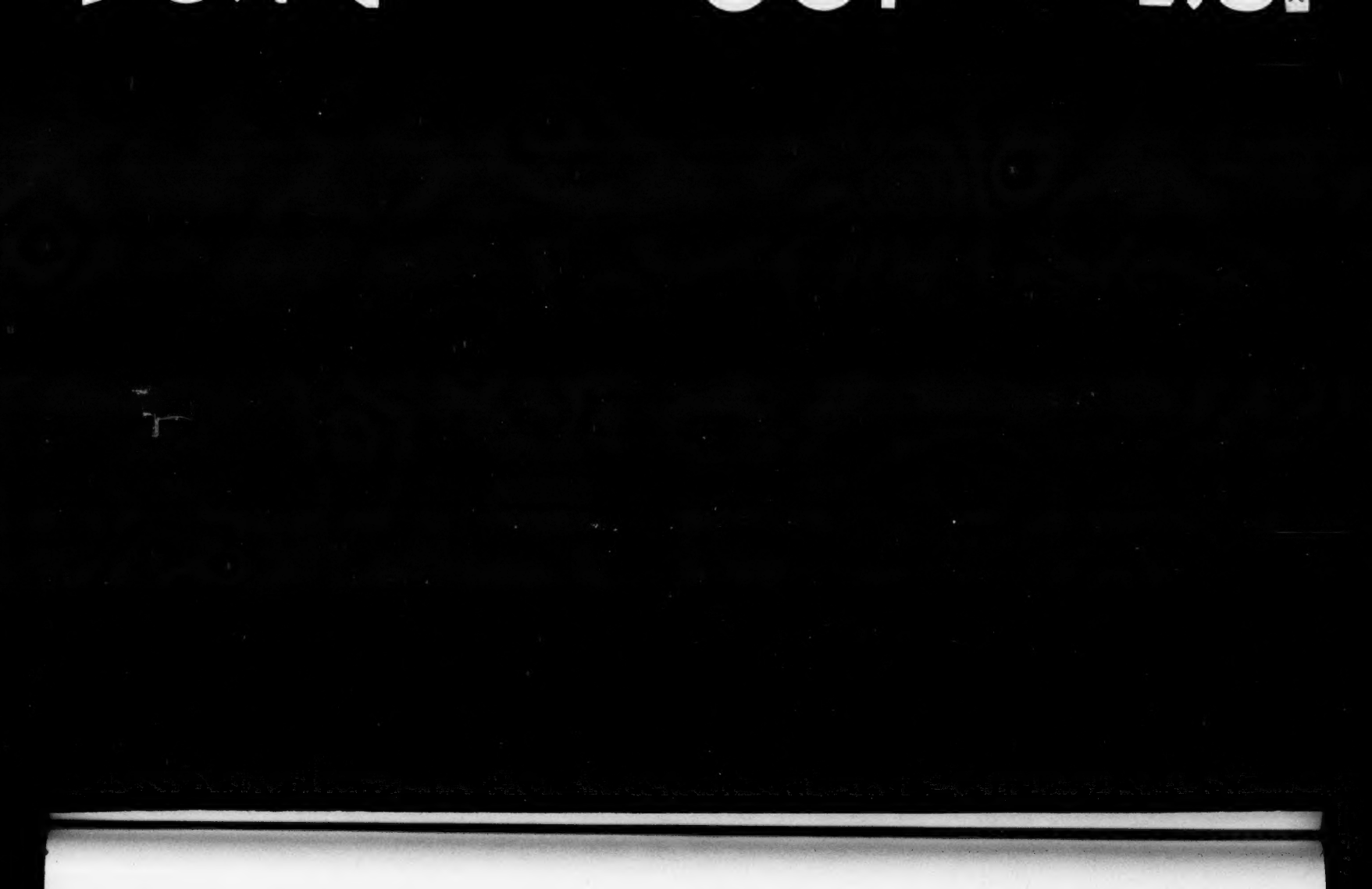
DR. RUBEN NOMLAND, Iowa City (by invitation): I agree with Dr. Michelson that the lesions presented are basically like those of morphea of the superficial type, which has many similarities to lichen sclerosus. I believe the microscopic pictures of superficial morphea and lichen sclerosus are identical. Therefore, we must go on clinical appearance. In lichen sclerosus et atrophicus there should be lesions elsewhere, some of which should be the typical small white papule.

DR. MARCUS R. CARO, Chicago (by invitation): My experience with this disease is the opposite of Dr. Nomland's. The section in lichen sclerosus et atrophicus shows a zone of edema just beneath the epidermis, a feature that I have never seen in sections of morphea. In the gross lesion of lichen sclerosus I have seen superficial hemorrhage several times but I have never observed this change in lesions of morphea. For this patient, on both clinical and histopathologic grounds, I would agree with the diagnosis of lichen sclerosus et atrophicus.

Cylindromatosis.

C. N., a woman aged 55 years, presents, scattered over her head, trunk and extremities, but more numerous in the center of the upper part of the back, many discrete superficial nodules varying in size from a few millimeters to several centimeters in diameter. These nodules are of a translucent flesh color with superficial telangiectasia, are firm and, nontender and appear almost to be "stuck on" the skin. There are no cafe au lait spots. There are a few nodules around the center of the face.

DISCUSSION

DR. S. W. BECKER, Chicago (by invitation): This condition is sometimes confused with von Recklinghausen's disease. I had a section sent to me some time ago with a diagnosis of von Recklinghausen's disease, but the microscopic picture was typical of cylindroma. A second tumor proved to be neurofibroma, and hence the patient had both disorders.

Localized Myxedema; Chronic Urticaria.
Acroscleresis.
Keratosis Follicularis.